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CONTROL OF VENTILATION

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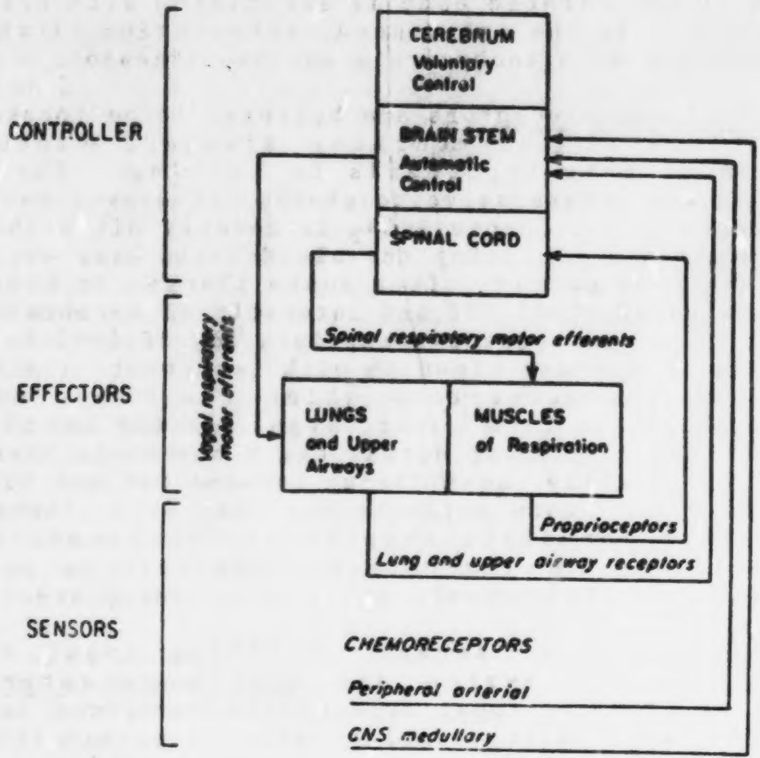
Regulatory and control mechanisms of ventilation normally function to meet the body's metabolic demands for oxygen uptake and carbon dioxide elimination. The purpose of this article is to discuss the organization and components of the respiratory control system and to briefly denote its adaptive responses to several physiological alterations.

The respiratory control system has three major components which include: (1) sensors, (2) effectors and (3) the controller. This concept is represented in Figure 1 and will be further discussed in the following sections.


CONTROLLER
CEREBRUM
Voluntary Control
BRAIN STEM
Automatic Control
SPINAL CORD
Spinal respiratory motor efferents
Vagal respiratory motor afferents
EFFECTORS
LUNGS and Upper Airways
MUSCLES of Respiration
Proprioceptors
Lung and upper airway receptors
SENSORS
CHEMORECEPTORS
Peripheral arterial
CNS medullary

NEJM 297:92-97, 1977

Figure I: Schematic representation of the respiratory control system

The respiratory control system has four types of sensors. These include peripheral chemoreceptors, central chemoreceptors, muscle receptors and receptors present in the lung and upper airways.

The peripheral chemoreceptors are the carotid and aortic bodies. The carotid bodies are located at the bifurcation of the common carotids and demonstrate increased chemoreceptor discharge in response to an increasing $PaCO_2$, a decreasing PaO_2 and a decrease in pH. They are almost entirely responsible for the hypoxic ventilatory drive. The location of the aortic bodies is less well defined. They demonstrate an increased chemoreceptor discharge with an increasing $PaCO_2$ or decreasing PaO_2, but they are not responsive to pH changes. Both sets of chemoreceptors demonstrate an increased output in response to hypotension and increased sympathetic activity. Circulatory responses mediated by the two sets of peripheral chemoreceptors differ in that stimulation of the carotid body is associated with bradycardia and hypotension. On the other hand, stimulation of the aortic body is associated with tachycardia and hypertension.

The central chemoreceptors are believed to be located on the ventral surface of the medulla, however, histological confirmation of this hypothesis is lacking. The central chemoreceptors are unresponsive to changes in oxygen tension, but do sense changes in pH. Because CO_2 is readily diffusible across biological membranes including the blood-brain barrier, and $[H+]$ and $[HCO_3^-]$ diffuse poorly, often acute changes in blood pH are accompanied by paradoxical CSF and interstitial cerebral fluid pH values. For instance, an intravenous infusion of $[H+]$ in the form of HCl results in a lower blood pH with resultant stimulation of peripheral chemoreceptors which react by increasing ventilation which in turn lowers blood and CSF levels of CO_2. Since $[H+]$ is slow to diffuse across the blood-brain barrier, but CO_2 diffuses out readily (equilibrium between CSF and blood CO_2), a CSF alkalosis and blood acidosis may coexist. Therefore, it is evident that immediate respiratory responses to acute metabolic acidosis or alkalosis are mediated by peripheral chemoreceptors (carotid bodies), not central receptors.

The third form of sensor providing input into the respiratory control system are muscle receptors. The contribution of afferent input from muscle receptors is felt to prevent agonist-antagonist musculer activities, otherwise their contribution towards respiratory control is thought to be limited.

The fourth and last group of sensors providing input into the respiratory control system are those found in the upper airways and lungs. Sensors in the upper airways include those in the nose, epipharynx and larynx. In general, they are sensitive to chemical and mechanical stimuli, therefore, their stimulation results in various reflexes such as coughing and sneezing.

Lung receptors are of three types: (1) pulmonary stretch receptors (PSR), (2) irritant receptors, and (3) juxtapulmonary-capillary receptors (J-receptors). The pulmonary stretch receptors are responsible for mediating the Hering-Breuer inspiratory inhibitory reflex. These receptors are located in the smooth muscle of airways and are innervated by the vagus nerve. They are activated by the stretch on the airways due to large inspirations with tidal volume greater than one liter. Thus, they are not active during normal tidal breathing. Their action is to inhibit inspiration at large volumes in order to regulate the work of breathing. The irritant receptors are located between airway epithelial cells and are activated by chemical and mechanical stimuli. Stimulation results in reflex cough and bronchoconstriction. The J-receptors are located in the wall of the pulmonary capillaries. They are activated by pulmonary congestion and increases in pulmonary interstitial fluid volume. Their stimulation results in an increased minute ventilation.

The effectors of the respiratory control system include the respiratory muscles and their interconnected neural pathways. Discussion of this subject is beyond the scope of this article. A concise, but thorough review of the subject can be found in Chapter 5 of Murray's The Normal Lung (12).

The controller of the respiratory system resides in the CNS. It is functionally divided into two components: (1) the brainstem, responsible for automatic respiration, and (2) the cerebral cortex which is responsible for voluntary breathing. Brainstem control mechanisms reside in the pons and the medulla. The pons contains the pneumotaxic center (PAC) and the apneustic center (APC). The PAC functions to fine tune the respiratory pattern by establishing the threshold for respiratory cut off. It is also believed to mediate the respiratory response to the various sensory inputs such as hypoxia, hypocapnia, etc. The apneustic center contains the normal inspiratory inhibitory mechanisms which function during normal tidal breathing. Absence or dysfunction of the APC results in apneusis or a rhythmic pattern of respiration characterized by a prolonged inspiratory phase. The medulla is ultimately responsible for spontaneous respiration and its presence is necessary for automatic respiration to occur. It is capable of initiating respiration in the absence of higher brainstem function, however the respiratory pattern is best characterized as being gasp-like or ataxic. Two groups of respiratory neurons are situated within the medulla: the dorsal respiratory group (DRG) and the ventral respiratory group (VRG). Axons from the DRG project to the VRG and to the inspiratory motoneurons (phrenic motoneurons). Axons from the VRG project upon the motoneurons of the intercostal or accessory muscles. Projections from the DRG and VRG descend the spinal column in the ventrolateral tracts of the white matter to influence the motoneurons of respiration.

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Voluntary or behavior related breathing (i.e. talking, laughing, etc.) control resides in the cerebral cortex. Projections from the cerebral cortex descend to the motoneurons in spinal tracts separate from those of the DRG and VRG axons. The descending cortical tracts are found in the dorsolateral columns of the cord. In summation, the control of respiration is a complex process which allows the respiratory system to make adjustments in order to accommodate to the varied metabolic and physiological situations to which it is subjected.

Up to this point we have discussed the components of the respiratory system and their interactions as related to the control of respiration. The following sections will discuss the relationships between various physiologic conditions, such as hypoxia, hypercapnia, and acid-base disturbance, and their effects on respiration.

OXYGEN (3,4,12)

The primary oxygen chemoreceptor sensors are found in the carotid bodies. The hypoxic ventilatory drive (hypoxic sensitivity) is determined by the frequency of carotid body impulses in response to a decreased arterial blood pO_2. Figures 2A and 2B represent the results of an isocapnic hypoxia response test in normal individuals. During the test, arterial pCO_2 is maintained constant in spite of increased ventilation by adding CO_2 to the inspired mixture.

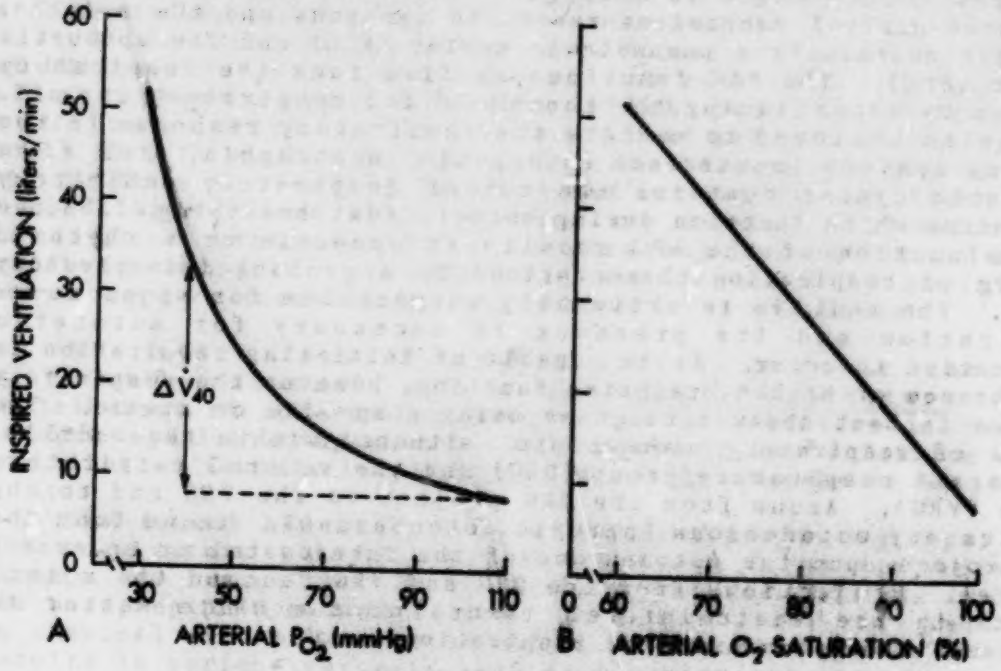

Figure 2: Isocapnic hypoxia response test
NEJM:297(4), p196, 1977

Conclusions from the latter figures can be summarized as follows:

(1) Ventilation begins to increase at arterial pO_2 values less than 100mmHg with significant increases at values less than 60mmHg.

(2) The relationship between arterial PO_2 and ventilation is hyperbolic, and

(3) The relationship between arterial oxygen saturation and ventilation is linear.

Hypoxic sensitivity is defined in several ways including $\Delta V/\%$ saturation which is represented by the slope in Figure 2 or $\Delta V40$ which is the change in ventilation when arterial pO_2 is decreased from 150torr to 40torr. Hypoxic sensitivity varies greatly, up to tenfold, in normal patients. Hypoxic sensitivity may be blunted or absent in the following conditions: (1) increasing age, (2) increasing altitude (acclimated), (3) opiates, and (4) COPD.

CARBON DIOXIDE (1,4,5,12)

The removal of metabolically produced carbon dioxide is another function of the respiratory system. The ventilatory response to CO_2 differs from O_2 in that only 12% of the hypocapnia hyperpnea response can be attributed to peripheral chemoreceptors with the remainder attributed to central chemoreceptors. As noted previously, CO_2 diffuses across the blood-barrier to combine with H_2O to form $[H+]$ and $[HCO_3^-]$. The $[H+]$ thus stimulates the central chemoreceptors. Carbon dioxide sensitivity is reported as the ΔV (change ventilation)/ ΔCO_2 mmHg (change in carbon dioxide tension). The CO_2 ventilatory response in normal healthy adults ranges from 2 to 5L/min for each 1 mmHg increase in pCO_2. The ventilatory response to CO_2 decreases with age, with sedatives, in endurance athletes and in COPD.

Having now discussed the control of respiration and the physiological response of the ventilatory system to oxygen and carbon dioxide, we will apply these principles to explain the ventilatory response to acid-base derangements.

ACUTE METABOLIC ACIDOSIS (6)

An example of acute metabolic acidosis would be diabetic ketoacidosis. In this example, ventilation is stimulated entirely by the peripheral chemoreceptors because [H+] diffuses through the blood-brain barrier poorly. A fall in pH from 7.4 to

7.2 will increase ventilation 2-3 times control. This hyperventilation leads to a reduced P_aCO_2. Acutely the reduced P_aCO_2 leads to a reduced CO_2 in the CSF and consequently a reduced [H+]. This alkaline CSF blunts the ventilatory response to acute metabolic acidosis. However, after 24 hours of metabolic acidosis, the HCO_3 in the CSF slowly leaks across the blood-brain barrier and the CSF pH is restored to near normal. At this time, the total ventilation may increase because the stimulation of the peripheral chemoreceptors by the low arterial pH is no longer opposed by the central chemoreceptors.

ACUTE RESPIRATORY ACIDOSIS

An example of acute respiratory acidosis would be a severe acute asthmatic attack resulting in CO_2 retention. In this setting there is a large ventilatory stimulus as the increased $PaCO_2$ stimulates both central and peripheral chemoreceptors.

CHRONIC RESPIRATORY ACIDOSIS

Chronic respiratory acidosis is best illustrated by the COPD patient with CO_2 retention (7). Under these conditions, the CSF pH has been restored to near normal. Thus, the elevated P_aCO_2 stimulates only the peripheral chemoreceptors which contribute only 12% of the respiratory response to CO_2. This may in part explain the blunted ventilatory response to elevated P_aCO_2 in some chronic "lungers". Other explanations for the decreased CO_2 response in some "lungers" with CO_2 retention include 1) severe mechanical limitation with tremendous work of breathing (can't breathe), 2) an abnormal central respiratory center response to CO_2 (won't breathe) (8).

A clinical example is the chronic "lunger" with P_aCO_2 of 70. Either the work of breathing is too high or the patient has a "defective" respiratory center. Regardless of etiology, when this patient is given excessive oxygen his hypoxic drive for ventilation is abated and he may stop breathing altogether. (The danger in this situation is real, and has been widely popularized, but it must be stressed that oxygen cannot be withheld from the critically hypoxic patient because of the fear of respiratory depression. The patient should be given a low concentration of oxygen, with ABGs repeated 15-20 minutes later, and above all he must be carefully observed.)

ACUTE METABOLIC ALKALOSIS (9)

An acute metabolic alkalosis may be precipitated by diuretics with a resultant contraction alkalosis and hypokalemia (9). In selected clinical circumstances, the decrease in peripheral [H+] may result in hypoventilation and mild CO_2 retention. This can be a serious problem in the COPD patient with pre-existing hypoventilation and CO_2 retention.

CHRONIC RESPIRATORY ALKALOSIS

A chronic respiratory alkalosis may be found in individuals exposed to high altitudes. Under these conditions, hypoxemia stimulates the peripheral chemoreceptors and respiratory alkalosis develops (10-11). Although controversy exists, some studies suggest that within 24 hours the CSF pH is restored to normal by the decrease in CSF HCO_3. By restoring the CSF pH to normal the hypoxic stimulus to hyperventilation is unopposed and the patient continues to hyperventilate.

SUMMARY

Ventilation is closely linked to both CO_2 production and O_2 consumption. In normal patients, the daily increases and decreases in ventilation are due chiefly to voluntary factors and the P_aCO_2. Hypoxemia is usually not a stimulus unless the PaO_2 is less than 60mmHg. The main mechanism for increased ventilation in response to rising levels of CO_2 is through the central effect of [H+] which stimulates an increased ventilatory rate.

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PULMONARY HOST-DEFENSE MECHANISMS

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The lung is arguably the most delicate of any major organ. When one considers that in excess of 10,000 liters of air invades the lung each day, the fact that most normal non-smokers will never experience lower respiratory disease is a tribute to the defense system and specifically to mucociliary clearance. The ability of a particle to penetrate host defenses is based in some part on its size. Figure 1 charts several particles of varying size against their sites of deposition, which correlate well with the respective condition or disease associated with each agent (1).

Figure 1

Substance	Particle Diameter (μm)	Site of Deposition
Cigarette smoke	<1 (much is hygroscopic)	Uncertain
City air pollution	<1 (usually aggregated, hygroscopic	Uncertain
Coal mine dust	1 to 7 (50% at 5μm)	Alveoli and ciliated airways
Rock dust (quartz)	1 to 7 (50% at 5μm)	Alveoli and ciliated airways
Staphylococci	10 to 14 (attached to skin scales)	Nasopharynx
Tubercle bacilli	2 (droplet nuclei)	Alveoli
Grass pollen	30	Nasopharynx
Fungal spores (e.g., *Alternaria*)	5 to 10	Large airways
Fungal spores (e.g., *Micropolyspora faeni*, *Aspergillus clavatus*)	1 to 5	Alveoli and smaller airways

*After Muir DCF, 1973.

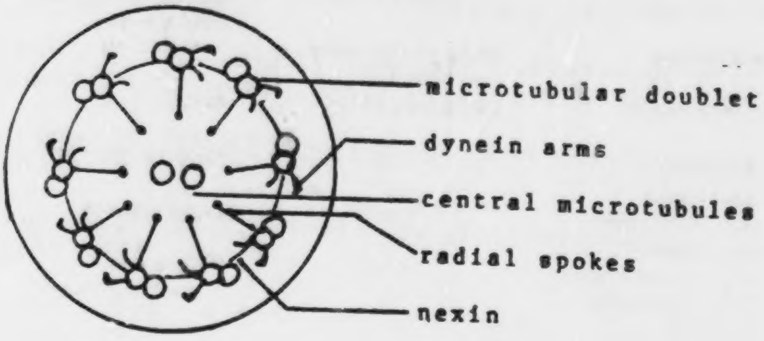
(from reference 1)

MUCOCILIARY CLEARANCE

Respiratory epithelium below the glottis begins in the proximal trachea and continues to the terminal bronchioles, the larynx being largely covered by mucus-secreting squamous epithelium. Mucociliary clearance is dependent on ciliated columnar and goblet cells, which constitute the greatest proportion of cells in the large airways, but which gradually diminish toward the periphery. Even in the trachea small areas are frequently found to be devoid of cilia, and even in "normal" airways small foci of squamous metaplasia can be found (2).

Each ciliated columnar cell is covered with about 200 cilia, measuring 7 microns in length and 0.2 microns in diameter. A normal cilium contains microtubules arrayed as a central pair of singlets and nine outer doublets. Radial spokes connect the central pair to the doublets, with nexin links connecting the latter to one another. Dynein arms protrude from each outer doublet, and are thought to provide the ATP needed for motility. (Figure 2) While this ultrastructure is typical for all mammalian mucus-propelling cilia, some defective cilia are seen even in normals, and samples from different sites in the bronchi can show substantial variation in the percentage of abnormals (3). Beneath the base of each cilium is a basal body, which is felt to play a role in initiating ciliary motion, even though the microtubules terminate above rather than in this structure.

Figure 2



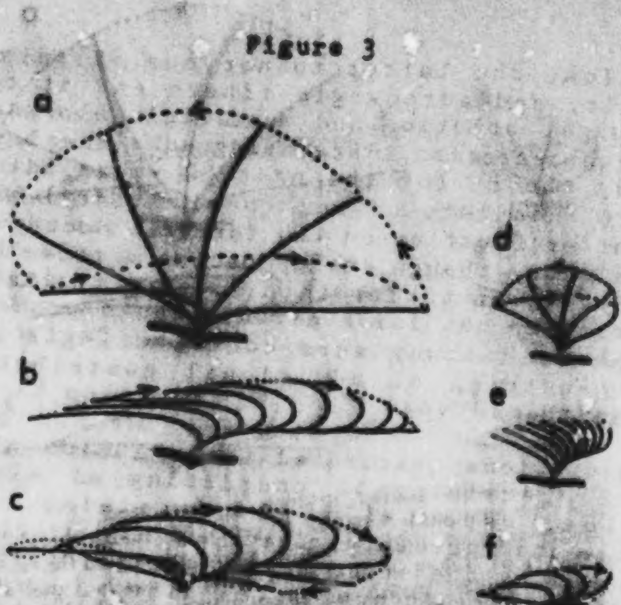
Mucus, normally up to 10 microns deep, is produced by goblet cells and submucosal glands. The former primarily respond to local irritation, the latter to nervous stimulation. Motor, parasympathetic, and adrenergic fibers end at the submucosal glands. Both vagal ablation and muscarinic blockade will reduce but not abolish secretion, indicating some basal secretory rate. The prevailing theory for the past 50 years has been that the mucus "blanket" consists of sol (periciliary) and gel (mucus) layers, the latter floating on the former. Mucus probably exists as rafts or islands, though it may become a true "blanket" in the central airways; even taking into account the faster transport time in the trachea, the large airways would probably be flooded if each peripheral airway were contributing a solid sheet of mucus, to say nothing of additional contributions from the central airways themselves.

Normal secretions, estimated to be 10-100 mls per day, are 95% water, the remaining 5% consisting of electrolytes and macromolecules, especially glycoproteins. The rheologic properties of sputum are determined largely by the concentration and more importantly the structure of the glycoproteins, which in turn is dependent more on number and site of crosslinks than by chemical composition (4). Normally disulfide bonds are relatively few in number so that mucus consists of predominantly linear macromolecules, resulting in a gel of low viscosity and high elasticity. Not surprisingly, using the isolated frog palate model, it has been found that mucus of high elasticity and low viscosity has the highest rate of transport, elasticity being the more important parameter (4); with very high elasticity, transport rates appear to decrease (6). A less elastic, more viscous medium, and hence a more sluggish medium, is seen when extensive lateral crosslinking occurs. The best example of this occurs in inflammation, where exudation of sulfhydryl-rich serum proteins leads to increased disulfide bonding. This model probably helps explain the indifferent results frequently obtained in clinical studies of mucolytic agents, since the indiscriminate reduction of bonds may as easily reduce elasticity as reduce viscosity.

Physiology

Cilia beat at about 1000 strokes per minute in humans, the motion beginning with a slow recovery stroke during which the cilium is flexed to one side, followed by a faster effective stroke with the cilium fully extended, with a brief rest period following that (7) (Figure 3). Ciliary beat frequency usually remains normal in airways disease (8), except for those specifically caused by defective cilia. The ciliary tip just enters the gel during the effective stroke and remains in the sol during the recovery phase. Cilia are coordinated metachronously, with stimulation of adjacent cilia during the recovery stroke (Figure 4). The actual mechanism of coordination between cilia is unknown, but it is probably not under nervous control in mammals. The overall direction of the effective stroke in the tracheobronchial tree is cephalad, but close scrutiny reveals small metachronal fields with slightly varying vectors.

Figure 3



1. Beat cycle of water-propelling cilium (Mytilu gill lateral cilium, 15 μ long) a, b, and c, compared with beat cycle of mucus-propelling cilium (rabbit tracheal cilium, 6 μ long), drawn to same scale in d, e, and f. In a and d stages of effective stroke drawn on dotted outline of path followed by ciliary tip as from side view. Recovery strokes seen from same position in b and e. Shapes and positions of cilia during cycles of beating viewed from above (c and f); paths followed by ciliary tips are shown dotted.

(from reference 40)

Figure 4

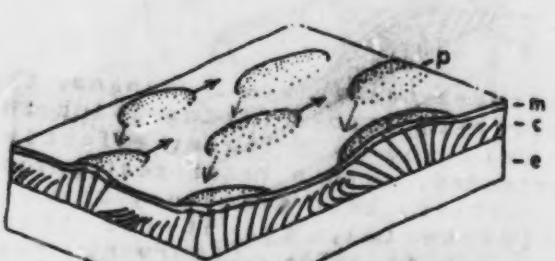


Diagram of small area of ciliated epithelium (e) propelling thin sheet of mucus (m). Cilia (c) perform curved recovery strokes in periciliary fluid beneath mucus, but penetrate lower side of mucus during their erect effective strokes. Effective cilia lift up mucus a little in these areas of application of propulsive force (p). Mucus is propelled in direction of *solid arrows*, but metachronal waves that propel it move in direction of *dotted arrows*.

(from reference 40)

Mucus velocity progressively increases from the peripheral bronchi to the trachea. Precise velocity is difficult to measure peripherally, but tracheal mucus velocity in normal young subjects is about 10-20 mm/min. This decreases with age, smoking, and drugs. The weight-carrying capacity of the ciliated epithelium is remarkable; no impairment in transport rate has been observed with weights up to 20mg per mm^2. (For the purpose of illustration, this would be equivalent to a 2cm depth of mucus.)

Techniques for measuring mucociliary function can be divided into two groups, those measuring the linear motion of some marker placed on the mucosal surface (mucus velocity or mucus transport), and those measuring the clearance of inhaled or insufflated materials (mucociliary clearance). Of the two, techniques measuring mucociliary clearance are generally simpler, but also involve certain assumptions and are more prone to error. All of these are predominantly research tools (9,10,11).

Factors Affecting Mucociliary Clearance

Certain reflexes have been shown to affect mucus production at least in animals. Chemical or mechanical irritation of the nose or nasopharynx increases mucus production. Mechanical stimulation of the larynx increases secretion, which may be part of the normal cough reflex. Gastric distention causes increased secretion, as does hypoxemia mediated via the carotid body. Transient lung inflation has been shown to decrease submucosal gland secretion, at least in dogs. There is evidence that alpha adrenergic stimulation increases serous secretion, while beta stimulation produces more mucoid secretions. Stimulation of the vagus depletes both serous and mucus cells, indicating more intense but non-specific stimulation (12). Interestingly, however, mucociliary clearance measured in patients with autonomic failure has been normal, implying that autonomic innervation is not necessary for function (13).

Because of the remarkable efficiency of the upper airway in adjusting the temperature and saturation of inspired air, changes in ambient air temperature and humidity have little effect on tracheobronchial clearance during normal breathing. Conversely saturation of inspired air with nebulized mist does not seem to stimulate clearance as long as coughing is suppressed. When the upper airway is bypassed by intubation or tracheostomy, clearance can be substantially impaired by inadequately humidified air. In dogs, bypassing the upper airway by use of an endotracheal tube has been found to lead to complete cessation of mucus transport in 3 hours; mucus velocity returned to normal after 3 hours of saturated 38^0 air. Further work in dogs has shown that 75% relative humidity is adequate to maintain normal function. To achieve this, air at 100% relative humidity must be warmed to at least 32° C. Temperature per se has little effect on clearance except for its effect on humidity. Although aggressive hydration has been recommended for years to promote mucus clearance in patients with obstructive disease, there is no hard evidence to support this recommendation. It is an assumption in part based on clinical experience with the marked increase in mucus viscosity seen in severely dehydrated patients. The effect of chest physiotherapy on mucociliary clearance is discussed in another chapter.

Tobacco smoke has been found to decrease mucus transport with acute and chronic use. In one study, 62% of young smokers showed significant decrease in tracheal mucus velocity, compared to 44% of ex-smokers - all had normal PFTs, including single breath nitrogen washout and helium-air flow volume curves. (14) Both particulate and gas phases have been incriminated, though nicotine probably plays an insignificant role. In dogs, filtration of cigarette smoke has been shown to ameliorate the depression of clearance only if a small number of cigarettes were smoked (15). Besides tobacco smoke, other atmospheric pollutants such as sulfur and nitrogen dioxides and ozone have been shown to produce ciliostasis and decreased mucus transport.

Although extreme hypoxia has been shown to produce reversible ciliary stasis, moderate to severe hypoxia that is still compatible with life has not been shown to have a significant effect. Hyperoxia, on the other hand, consistently impairs mucus transport, and appears to do so prior to the development of inflammation. In cats, tracheal mucus flow has been shown to inversely correlate with inspired oxygen concentration after only 20 minutes of exposure. Dogs show a similar response, but several hours of exposure is needed. In normal humans, 90% oxygen produces a 50% reduction in tracheal mucus velocity at 6 hours.

General anesthesia clearly depresses mucociliary clearance, probably one of the major factors leading to postoperative atelectasis (16-18). How much of the stasis is due to specific anesthetic agents is harder to determine, since the effects of mechanical intubation, inadequately humidified gases, and premedication must all be taken into account. One group has shown that positive pressure ventilation itself impairs clearance, which may help to explain some of the contradictory data (19).

Among therapeutic agents, beta agonists have received the most attention. In general, all the beta agonists studied have been shown to increase clearance and mucus velocity in normals and COPD patients. In normal subjects clearance is often doubled while in obstructive disease clearance is definitely increased, though never to normal (20,21). A few studies of bronchitics have failed to show any effect from a beta-2 agent (22); however, these studies have most often utilized radioisotope clearance, with inadequate correction for central deposition and/or alveolar clearance fractions. Beta agents appear to exert their effect by a dose-dependent increase in ciliary beat frequency and by secretolysis. Propranolol has been shown to decrease clearance in normal lungs, an effect not seen with metoprolol or pindolol (23).

Atropine has been shown to decrease tracheal mucus velocity in normal humans. Ipratropium, however, has been found to have no effect in dogs, while in humans mucociliary clearance (MCC) may even increase (24). In any case, neither agent has ever been shown to have a deleterious clinical effect in bronchitics (25). No clearance studies per se have been done in bronchitics using these agents, since many of these patients have tracheal mucus velocities near zero.

Aminophylline in vitro increases ciliary beat frequency and enhances secretion. In vivo both in animals and humans, it has been shown to enhance mucus velocity and clearance (26,27).

Mucolytic agents have shown either a small or more often no effect in increasing clearance. Steroids have generally shown no effect either, though a small increase in ciliary beat frequency has been demonstrated (28). Narcotics uniformly depress mucus transport, as does ethanol, although one recent study failed to demonstrate a consistent effect (29). Aspirin has been shown to slightly decrease (30), and cardiac glycosides to increase, mucus transport.

Disease states

Although mucus transport has not been studied during acute pyogenic infections of the lower respiratory tract, impaired transport has been clearly demonstrated following viral and Mycoplasma infections. Following infection by influenza A, mucociliary clearance has been found to be depressed for as long as six weeks. Clearance has been found to be retarded following M. pneumoniae infections, and to remain partially depressed for up to one year afterwards (2).

Chronic bronchitics almost uniformly demonstrate profound reduction in clearance, with tracheal mucus velocity generally in the range of 1 mm/min. In general, cystic fibrosis patients appear to be similar. Although sputum from "cystics" is biochemically distinctive in having larger amounts of acid glycoproteins, most investigators have been unable to show any significant difference in rheologic properties from that of bronchitics. Impairment of ciliary function through a ciliotoxic serum factor has been postulated for 20 years, with evidence for and against, but ciliary beat frequency is usually normal (31). Tracheal mucus velocity is frequently comparable to bronchitics, but is occasionally normal and does not correlate with disease severity (32).

Sputum from asthmatics with active disease is generally more viscous than in any other disease group (33). Asthmatics in full flower have mucus velocities about 10% of normal. Clearance even in remission is impaired; in one study of young patients in remission from allergic asthma, tracheal mucus velocity (TMV) was 55% of normal (34). Challenge with specific antigen yielded a further 50% decrease in TMV, which persisted after specific airway conductance returned to normal. Similar results have been found in *Ascaris* sensitized dogs; an aerosol of *Ascaris* produced slowing of transport in all dogs, whereas bronchospasm occurred in only half, and the mucociliary effect lasted longer (2). In canine and human models, inhibition of leukotriene C prevents the slowing of mucus transport following challenge, without affecting bronchospasm (35).

Immotile cilia syndrome, of which Kartagener's is probably a subset, was first described in 1977 (36). Since then motile cilia have been demonstrated in all these patients; although in some the numbers of motile cilia are low, the common factor seems to be ineffective or incoordinated motion (37,38). For this reason, dyskinetic cilia syndrome is probably a better term. Although the initial group of patients were found to have defective dynein arms by EM, other subgroups have since been described with defective radial spokes (39), transposition of microtubules (40), and most recently with excessively long cilia (41). A study by Rossman et al correlated the structural abnormality with distinctive types of ciliary motion (42) Symptoms in all patients are similar - upper respiratory symptoms are the predominant and earliest manifestations, consisting of frequent nose-blowing, recurrent sinusitis, and chronic secretory otitis media. Sterility typically occurs in males due to defective motility of spermatozoa; sperm and cilia are not always equally involved, however, some patients having respiratory symptoms without sterility (43). Although it is possible to diagnose the syndrome prior to the development of bronchiectasis, it is doubtful that intervention at any earlier stage would significantly alter the clinical course.

OTHER METHODS OF CLEARANCE

In addition to mucociliary clearance, other mechanisms are involved in the clearance of inhaled particles. Bronchoconstriction occurs with irritation of the nose, larynx, or trachea by mechanical or chemical means. Although usually viewed as a nuisance or worse, such a response may play a role in preventing deeper penetration by various irritants (44). There is some corollary to this in coal-workers' pneumoconiosis, in that less dust appears to be deposited in those parts of the lung more affected by bronchitis (45).

Cough is an emergency mechanism in normals, but may be the prime method of clearance in patients with airways disease. It

[illegible]
[illegible]
[illegible] foreign bodies
begins with deep inspiration, followed by glottic closure and contraction of expiratory muscles generating large pleural pressures (often greater than 100mmHg). The sudden opening of the glottis begins a forceful stream of air, and because of the sudden drop in pressure in the airways there is partial bronchial collapse. This leads to a high linear velocity of airflow in the central airways which tends to shear secretions or foreign bodies off the bronchial walls and propel them through the glottis. Cough is much less effective in peripheral airways, because of the larger total cross-sectional area and because of the lower pressure drop from the alveoli to those airways. However the compression of these airways during coughing may create a milking action, driving secretions into larger airways (45). Although cough is often the only effective means of clearance in patients with obstructive airways disease, it is not as efficient as it is in normals. This is due to the closure, rather than just narrowing, of distal airways during the cough and to the viscous nature of the secretions.

CELLULAR/HUMORAL DEFENSE MECHANISMS

Alveolar macrophages constitute the last line of defense against inhaled particulate matter. Both animate and inanimate foreign bodies are engulfed by the cell, with lysosomes subsequently fusing with the phagocytic vesicles to form phagolysosomes. Within these vesicles, proteolytic and hydrolytic enzymes act together with toxic oxygen radicals to digest particles. When the inhaled particles are microbes, a number of more complex mechanisms come into play. Neutrophils are recruited from peripheral blood by a variety of chemotaxins, some derived from alveolar macrophages, others arising from lymphokines, bacterial sources, and complement fragments, to name a few (46,47).

Immune responses assume an important role when non-specific phagocytic mechanisms prove to be inadequate. Macrophages and lymphocytes appear to be highly dependent on one another to mount an effective defense against infection. Macrophages may induce both B- and T-cell responses by processing and presenting foreign antigenic material to both types of lymphocytes, which differentiate into plasma cells and "killer" lymphocytes respectively. In turn, lymphocytes play a central role in the activation of macrophages, resulting in a macrophage with greater phagocytic capabilities and a higher lysosomal content, and displaying greater activity toward all foreign material, not just the specific antigen which induced the response (48).

Throughout most of the respiratory tract, secretory IgA is the predominant antibody on mucosal surfaces, though there is evidence to suggest that IgG may be present in greater quantity in the smaller bronchioles and alveoli (49). Also, while IgA secreting cells are the predominant type in most of the bronchial tree during health, IgG and IgM plasma cells may predominate in disease states. While only small numbers of IgE secreting cells are present in the airways, the relative proportion of these cells is higher than in most tissues, possibly explaining why allergic manifestations so frequently involve the respiratory system.

The exact role of IgA is not clear, though certain effects are known. It is formed in large amounts in response to antigenic stimulation and is capable of neutralising toxins, e.g. cholera toxin (50). IgA-deficient patients have a high incidence of serum antibodies to dietary antigens, leading some to surmise that IgA may play a role in limiting the absorption of foreign antigen. The higher incidence of autoimmune diseases in these patients tend to support this (51). While IgA deficiency is associated with an increased risk of respiratory infections and allergic disorders, many asymptomatic patients have also been identified; in most cases they appear to have replaced IgA in normal secretions with IgM (52).

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ESSENTIALS OF PULMONARY FUNCTION TESTING

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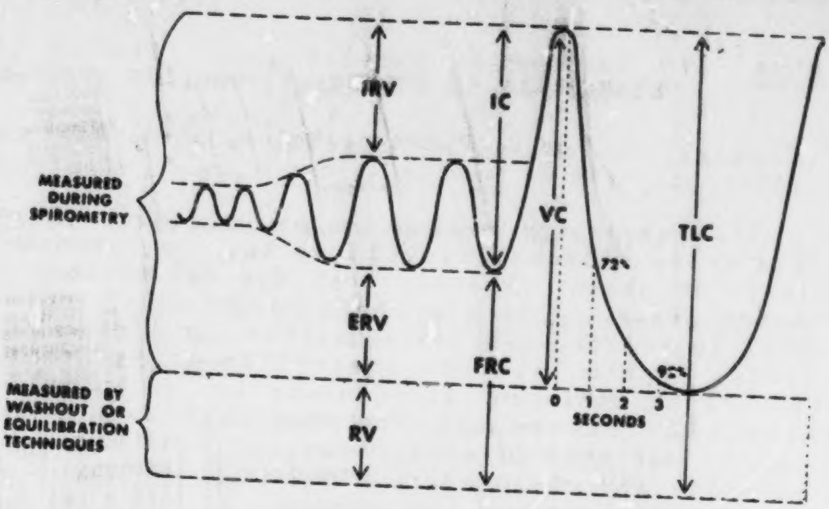
The laboratory evaluation of pulmonary diseases is nearly unique among medical disciplines for the remarkable amount of information about function that may be obtained from minimally invasive tests. Like the chest radiograph, pulmonary function testing is generally quite sensitive for the presence of disease, although again like the chest film it is considerably less effective at differentiating among the potential causes. While nearly all test results in the pulmonary function lab are objective and quantifiable, most do require a degree of patient cooperation and will frequently be misleading if the patient is unable or unwilling to cooperate.

The primary function of the respiratory system is to bring a constant supply of humidified air into intimate contact with the cardiac output for the purpose of oxygen and carbon dioxide exchange. The ventilation side of this system consists of branching airways leading to the exchange surface, with flow powered by respiratory muscles. A number of practical methods have been devised to test various portions of this ventilation limb. Testing the function of the perfusion limb is less practical and generally more invasive, although, since they are partially perfusion dependent, diffusion capacity and blood gases provide a rough evaluation. With the exception of arterial blood gases, the pulmonary function tests most commonly obtained are spirometry, static lung volumes, and diffusion capacity. This chapter will deal primarily with the methods and interpretation of those studies. For a more detailed discussion of physiology, a number of sources are noted in the references.

SPIROMETRY

Spirometry as it is presently used is the volume-time analysis of airflow. This was not always the case; until thirty years ago, the spirometer was used primarily to measure a series of lung volumes, which are still of clinical importance and are illustrated in the following diagram.

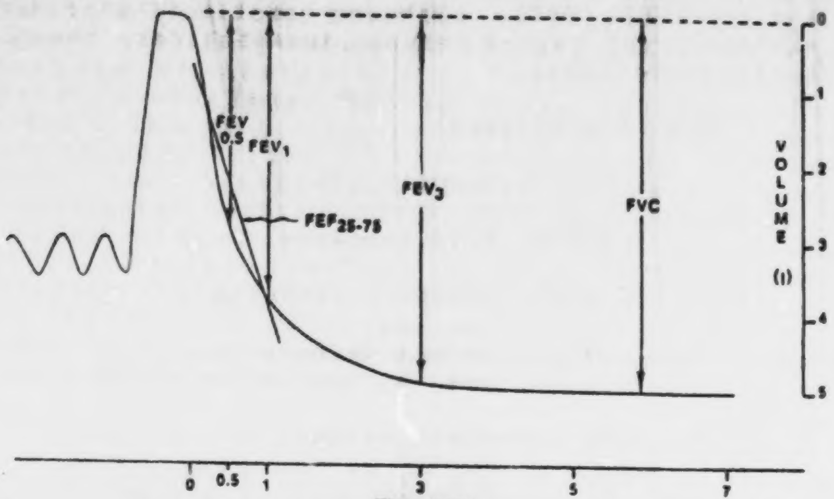
Figure 1


MEASURED DURING SPIROMETRY
IRV
IC
VC
TLC
72%
ERV
FRC
92%
0
1
2
3
SECONDS
MEASURED BY WASHOUT OR EQUILIBRATION TECHNIQUES
RV

TLC = total lung capacity; VC = vital capacity; IC = inspiratory capacity; FRC = functional residual capacity; IRV = inspiratory reserve volume; ERV = expiratory reserve volume; RV = residual volume. A capacity is composed of two or more volumes added together.

Though some are rarely obtained, all the volumes and capacities illustrated can be measured by conventional spirometry, except those containing RV. (Since TLC is among these, restrictive disease cannot be reliably diagnosed by spirometry; methods for measuring TLC are covered in the following section.) In the past, spirometric volumes were usually obtained by slow maneuvers, the slow vital capacity being the commonest. If instead the patient is instructed to perform a full inspiration and then to exhale as rapidly and forcefully as possible, one obtains a curve known as a forced vital capacity which is illustrated in Figure 2.

Figure 2



Normal forced expiratory spirogram with FEV$_{0.5}$, FEV$_1$, FEV$_3$, and FEF$_{25-75\%}$. Expiration is almost complete after 3 sec.

Since air trapping can lower the measured vital capacity and is exaggerated during rapid exhalation, the forced maneuver is not as accurate at measuring VC. However it is now much more commonly employed, since the most useful application of spirometry in modern pulmonary practice is for detecting expiratory flow obstruction.

By strict definition, spirometry doesn't actually quantitate obstruction, since it doesn't measure resistance. Spirometry measures change in volume over time, i.e. flow. To actually measure resistance, the pressure drop would have to be known. In this case that is equal to intra-alveolar pressure, since downstream pressure is atmospheric, but intra-alveolar pressure is not easily measured. Clinically useful spirometry is performed under conditions of maximal effort. When that is achieved, correlation of normal flows to anthropometric data is sufficiently close to establish predicted values. Normal flow is related directly to height, inversely to age after adulthood, and is higher in males and Caucasians. Clearly, to be of any value, spirometry must be performed using maximal effort, which should be critically evaluated by the technician and confirmed by examination of the tracing itself. The expiratory tracing should be smooth, without notching, and sustained for 5-6 seconds; it should also be reproducible within 10-15% variation on at least two trials.

Although any number of mathematical calculations may be derived from a complex curve like the expiratory spirogram, only three measurements are of much use: the forced vital capacity (FVC), the forced expiratory volume in one second (FEV_1), and the ratio of the two (FEV_1/FVC). Although quantitation of defects is somewhat arbitrary and varies between institutions, the following are reasonable guidelines.

FVC (% predicted)

80-120	normal
70-79	mild decrease
50-69	moderate decrease
<50	severe decrease

FEV_1/FVC (absolute ratio)

>75	normal
60-75	mild obstruction
50-59	moderate obstruction
<50	severe obstruction

The FEV_1/FVC ratio is reasonably specific for diagnosis of airways obstruction, and a normal FVC is useful for ruling out restrictive disease, assuming of course that they are derived from a maximal effort curve. The following rules are of value in interpreting spirometry:

1. A normal FVC rules out significant restriction.

2. An abnormal FEV_1/FVC reliably indicates airway obstruction.

3. A normal FEV_1/FVC rules out significant obstruction if the FVC is normal.

4. In the presence of a reduced FVC, the FEV_1/FVC ratio usually underestimates the degree of obstruction to an unquantifiable degree.

5. For a change to be considered significant (over time, or following a bronchodilator challenge), a difference of 15% in the actual FEV_1 is required.

6. If the tracing suggests submaximal effort, interpretation is largely useless.

An inhaled bronchodilator should be administered if the FEV_1/FVC or FVC is low, followed by repeat spirometry 15-30 minutes later. Although a change in FEV_1 indicates significant reversibility of obstruction, failure to respond to a bronchodilator challenge should never preclude a trial of bronchodilator therapy, since patients may respond to several weeks of therapy after failing a single inhaled dose. Furthermore, the beneficial effects of these drugs are not limited to bronchodilation. Given that, why perform the maneuver in the first place? There are several areas where the bronchodilator challenge may be of use: in prognosis; in differentiating possible air trapping from restrictive disease, if a low FVC reverts to normal after the challenge; and in preoperative management, where a post-drug response suggests that further benefit may be gained by more aggressive "buffing".

In addition to the three values discussed above, a variety of numbers may be calculated from the forced vital capacity maneuver, but few are of interest and none of much use. For some years, the maximal mid-expiratory flow rate, now more commonly called the FEF25-75 (forced expiratory flow between 25% and 75% of exhaled volume), has been touted as a screening test for early COPD. Since most airways resistance occurs in larger airways, and since there is evidence that obstructive disease begins in smaller airays (<2mm), the FEV_1/FVC is not an early indicator of disease. With the decrease in transpulmonic pressure occurring throughout exhalation, the point of greatest resistance tends to move peripherally, so that the mid-portion of the expiratory curve is felt to reflect resistance in smaller airways. It would seem, therefore, that the FEF25-75 might be an early predictor of small airways disease. In actual practice, however, the range of normal is so great that to be abnormal the value must be less than 50% of predicted. The low value must also occur in conjunction with a normal FEV_1/FVC, since otherwise gross airways obstruction already exists. Thus a normal FEV_1/FVC coupled with a FEF25-75 that is 50% of predicted requires that flow in the first 25% of exhalation be extraordinarily high - altogether a rare combination of events.

Although peak expiratory flow is more properly derived from a peak flow meter, it is often calculated from spirometry. Peak flow is of little use in diagnosis, since it is highly dependent on effort, with no reliable way to judge the effort at that instant in time. In addition, it can be falsely elevated in obstructive disease by the sudden compression of large airways at the start of exhalation. This is not to belittle its use in following obstruction - in the acute treatment of an asthmatic a drop in peak flow is still significant even if due to flagging effort.

Although not normally derived from the forced vital capacity maneuver, maximal voluntary ventilation (MVV) is also performed on a spirometer, by having the subject breathe as quickly and deeply as possible for 10-12 seconds and then extrapolating this value to one minute. Of little use in diagnosis, there is a rationale for its use in preoperative patients, since the host of variables which may affect it (muscular disease, neurologic disease, deconditioning, and poor effort, as well as airways disease) also affect postoperative morbidity and mortality.

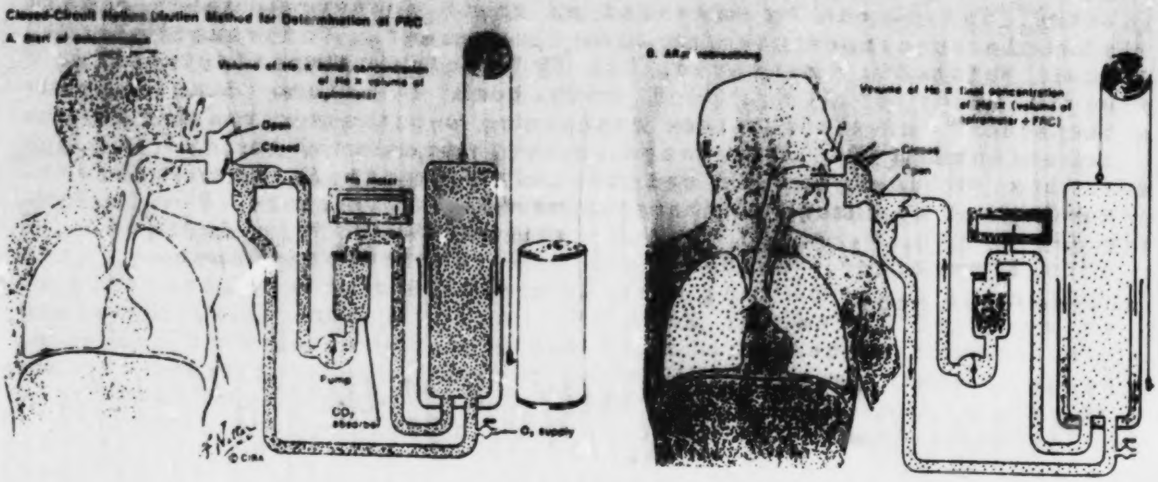
STATIC LUNG VOLUMES

Spirometry is incapable of measuring residual volume or any capacity which includes residual volume, i.e. FRC and TLC. To diagnose and follow restrictive diseases, and to differentiate air trapping from restriction as a cause for low vital capacity, it is necessary to measure one of these three values to calculate true lung volumes. In actual practice measurement of RV is more difficult and less accurate, so that TLC or more often FRC is the value directly measured; other values are then calculated from spirometry. The techniques generally available are roentgenographic planimetry, inert gas dilution or washout, and body plethysmography.

Planimetry measures total lung capacity by measuring lung area on PA and lateral radiographs and then calculating lung volume from those values. It is somewhat time-consuming, and depends on the x-ray technician to ensure that both radiographs were really taken at TLC. On the other hand it is inexpensive, and since it measures trapped air as well as functioning lung volume it is a reasonably close second to plethysmography in accuracy.

Gas techniques involve dilution or washout of biologically inert gases (helium and nitrogen, respectively) by either multiple or single breath methods. Whatever the method, the principle is largely the same, i.e. a gas which for practical purposes is neither absorbed from nor excreted into the lungs is diluted from a known original concentration to a final measured concentration and volume. Since the amount of the gas is assumed to be constant, the original volume can be calculated by $C_1V_1 = C_2V_2$. The test must be uninterrupted, and conducted with a closed system. Most of these methods measure FRC.

Figure 3

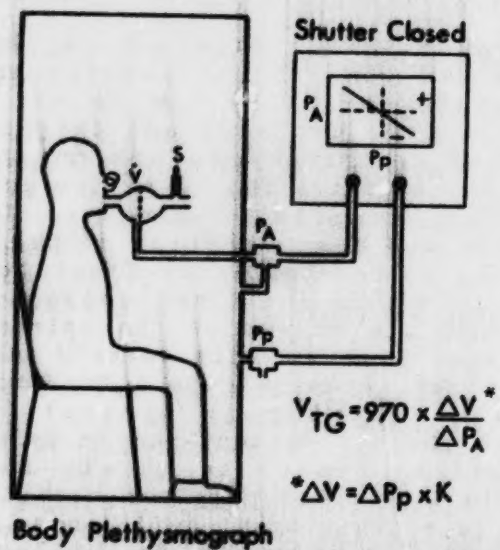

Closed-Circuit Helium Dilution Method for Determination of FRC
A. Start of determination
Volume of He = initial concentration of He × volume of spirometer
Open
Closed
He meter
Pump
CO₂ absorber
O₂ supply
B. After rebreathing
Volume of He = final concentration of He × (volume of spirometer + FRC)
Closed
Open

from Reference 1

Multiple breath helium dilution is the most frequently performed. From FRC the subject inhales and exhales from a spirometer containing 8-10% helium in air. Exhaled CO_2 is absorbed by a soda lime canister and oxygen is bled into the system to keep end-expiratory volume constant. Rebreathing continues until the concentration of helium in the expired gas is relatively constant, usually 4-7 minutes. In this method, the initial gas volume and concentration of helium are known (i.e. the contents of the spirometer), the final helium concentration is measured, and from this the final volume of distribution can be calculated. When the volume of the spirometer is subtracted from this, the result is FRC - with certain limitations. A fault common to all the gas techniques is a tendency to underestimate FRC whenever air trapping is present, because of poor equilibration with the air sequestered in bullae. Since a major (probably the major) reason to obtain lung volumes is to differentiate between air trapping and restrictive defects when FVC is low, this is a significant deficiency. On the other hand, gas techniques are satisfactory to follow the progress of interstitial diseases, and the underestimation of trapped air can be put to good use when calculating the percent of trapped air in the lungs prior to considering surgical bullectomy.

Plethysmography is the gold standard for measuring lung volume, employing Boyle's Law to calculate FRC. This law states that at constant temperature, the volume of a gas within a closed container varies inversely with the pressure to which it is subjected, thus $P_1V_1 = P_2V_2$. V_1 is the value sought, P_1 is known (i.e. barometric pressure, which by the way cannot be taken as zero), and p_2 can be measured as mouth pressure, which equals alveolar pressure when no flow is present. Unfortunately, V_2 can't be readily measured, but by placing the patient inside a rigid "body box" equipped with both a volume displacement transducer and a mouthpiece containing a pressure transducer, the relationship of ΔP (change in mouth pressure) to ΔV (change in box volume) can be calculated. Change in box volume is equivalent to change in thoracic volume. From there, $P_1V_1 = P_2V_2 = (P_1 + \Delta P)\ (V_1 + \Delta V)$, and V_1 can eventually be derived. In actual practice, rather than one respiratory maneuver, the patient is asked to pant against a closed shutter, resulting in an averaged value for $\Delta P / \Delta V$. Also, rather than a volume displacement transducer, which has a poor frequency of response, boxes are usually equipped with a pressure transducer and changes in box pressure are converted to changes in volume by a calibration factor dependent on box size and patient size.

Figure 4



Shutter Closed
P_A
+
−
P_P
S
$\dot{V}$
P_A
P_P
$V_{TG} = 970 \times \frac{\Delta V}{\Delta P_A}^{*}$
$^{*}\Delta V = \Delta P_P \times K$
Body Plethysmograph

This model illustrated the physical method of calculating lung volume (V_{TG}). The relationship (K) between volume change (ΔV) and pressure change in the box (ΔP_B) is determined so that pressure changes can be used to determine volume changes. When the shutter (S) is closed at FRC, the subject tries to inspire and expire so that the air in the chest is decompressed and compressed. As the chest volume increases the box volume decreases, and vice versa. The relationship between the mouth pressure (P_A) and the pressure in the box (P_B) is plotted on an oscilloscope. Since the pressure in the lungs at end-expiration was 970 cm H_2O. $V_{TG} = 970 \times \frac{\Delta P_B \times K}{\Delta P_A}$.

from Ref 2

Plethysmography is quite accurate, measuring lung volume regardless of air trapping. Temperature is a minor problem - by Boyle's Law it must be constant, but this is achieved reasonably well prior to beginning the study by continually venting the box until the pressure levels off. Practically, the biggest difficulty consists of putting a patient into a box little larger than a coffin, sticking a rubber mouthpiece between his teeth, and expecting him to relax to FRC. This difficulty can usually be overcome by a trained technician, who will observe the patient carefully and suddenly close the shutter when he appears to have relaxed.

DIFFUSION CAPACITY

Actually something of a misnomer, diffusion capacity measures the overall gas exchange function of alveolo-capillary units, of which membrane diffusion characteristics only play a part. DLCO is commonly referred to in Britain as transfer factor, a more accurate term.

In the more common single breath method, the subject takes a full vital capacity inspiration (composed of 0.3%CO, 10% helium, 21% oxygen, and 69% nitrogen), holds his breath for 10 seconds, then exhales. The first liter of exhaled gas is discarded as dead space, and the concentrations of CO and helium are measured in the remaining gas. The use of helium in the mixture allows the calculation of the initial carbon monoxide concentration in the lung, since the inhaled gas is diluted by the residual volume, and also allows a correction for alveolar volume (DLVA). A low DLCO and normal DLVA indicate a decrease in quantity rather than function of alveolo-capillary units (e.g., following lobectomy).

While sensitive to early interstitial diseases, DLCO is somewhat limited in its use by a lack of specificity - a number of other factors, both pulmonic and extrapulmonic, may affect it. In general anything which increases the number of red blood cells in the pulmonary capillary bed during the breath-holding period will increase CO uptake. Polycythemia, mild CHF, left to right shunts, pulmonary hemorrhage, and exercise will all elevate DLCO. Sometimes asthma will as well, though this is poorly understood. Anemia, severe CHF, emphysema, increasing age, and female sex all decrease the value. DLCO must be measured sitting, since standing decreases pulmonary capillary blood volume, thus lowering the measurement. Probably it is best used to follow the progress of infiltrative diseases, or to detect them at an early stage in high risk populations (e.g. P. carinii pneumonia in AIDS).

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ARTERIAL BLOOD GASES

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Arterial blood gases are invaluable in the assessment and management of patients with respiratory disease and acid-base disorders.

Three independent direct measurements are made on an arterial blood gas (ABG) sample. They are the PaO_2 (partial pressure of O_2 in plasma), the $PaCO_2$ (partial pressure of CO_2 in plasma) and the pH (the negative log of [H+]). The PaO_2, $PaCO_2$ and pH provide information about oxygenation, ventilation and acid-base balance. The reported HCO_3 and base excess are calculated from the direct measurements of PaO_2, $PaCO_2$ and pH. O_2 saturation should preferably be measured, but is often calculated instead

OXYGENATION

Arterial Oxygen Tension (PaO_2)

The PaO_2 measures the partial pressure of O_2 dissolved in plasma. The solubility coefficient of O_2 is 0.003cc per mmHg partial pressure of O_2, therefore the PaO_2 measures the smallest fraction of the blood's total O_2 content. Hemoglobin (Hgb) bound O_2 accounts for the majority of total O_2 content. We may calculate total O_2 content using the following formulas:

Hgb bound O_2 = Hgb g/dl x 1.34 cc/g x % saturation of Hgb
where 1.34 cc/g equals the O_2 carrying capacity of hemoglobin.

Dissolved O_2 = 0.003 cc/mmHg x PaO_2 mmHg

Total O_2 content = bound O_2 + dissolved O_2

With a hemoglobin of 15 g/dl, a hemoglobin saturation of 98%, and a PaO_2 95, the total O_2 content of 100cc's of blood is approximately 20 cc's of O_2, 98.6% of which is hemoglobin bound.

While the PaO_2 measures only the smallest fraction of total O_2 content, it is easily measured and allows us to estimate hemoglobin saturation at a given pH and temperature. Remember that pH and temperature changes shift the O_2 dissociation curve (Figure 1).

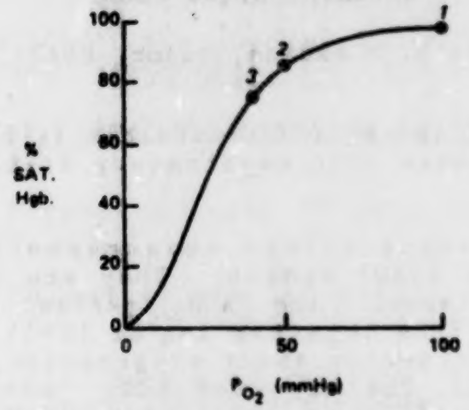

Figure 1

The clinically important variables in assessing oxygenation are hemoglobin saturation, total O_2 content, and O_2 delivery. Saturation and content may be estimated from the PaO_2, or may be directly measured. O_2 content is affected by conditions producing hypoxemia (discussed later), by anemia, and by displacement of O_2 from hemoglobin (as in carbon monoxide poisoning). Note that in the latter two conditions total O_2 content may be severely depressed and yet the PaO_2 may remain normal. O_2 delivery is the product of O_2 content and cardiac output, the discussion of which is beyond the scope of this chapter.

The normal value for PaO_2 decreases with age and may be calculated from the following formulas:

Seated $PaO_2 = 104.2 - 0.27 \times \text{age}$

Supine $PaO_2 = 103.5 - 0.42 \times \text{age}$

The decrease in PaO_2 with increasing age is the result of the development of low V/Q units. This is probably secondary to the loss of elastic recoil of the lung with age.

Alveolar Oxygen Tension (PAO_2)

Arterial oxygen tension is dependent upon alveolar oxygen tension, ventilation, perfusion and diffusion across the alveolar-capillary membrane. An understanding of alveolar oxygen tension and the alveolar-arterial O_2 gradient (A-a DO_2) is essential to interpreting blood gas data.

Dalton's law states that in a gaseous mixture the sum of the partial pressures of each gas in the mixture equals the total pressure of the mixture. For atmospheric air, barometric pressure (or alveolar pressure) equals the sum of the partial pressures of major atmospheric gases.

$$P_B \text{ or } P_A = P_{N2} + P_{H2O} + P_{CO2} + PO_2$$

Since the partial pressures of nitrogen and water are relatively fixed, the variation in partial pressures of O_2 (PO_2) and CO_2 (PCO_2) determine alveolar pressure. As a result, PAO_2 and $PACO_2$ have an inverse relation given a constant alveolar pressure.

The PCO_2 in inspired air is negligible and may be ignored. During expiration the PCO_2 in expired air rapidly increases, such that at end expiration it equals $PACO_2$, which in turn equals $PaCO_2$ because of the rapid transcapillary diffusion of CO_2 (20 times that of O_2). $PaCO_2$ may therefore be substituted for $PACO_2$ in determining alveolar pressure.

Using Dalton's law, and substituting $PaCO_2$ for $PACO_2$, the alveolar air equation may be derived:

$$PAO_2 = (P_B - 47)\ FiO_2 - PaCO_2/0.8$$

The partial pressure of any gas in a mixture is determined by multiplying the fractional percent of that gas (in this case FiO_2) times the total system pressure (P_B). The stated FiO_2 for any gas mixture is only accurate in the absence of water vapor; therefore for humidified air (as in the alveolus) water vapor pressure (47mmHg) must be subtracted from P_B. The correction factor of 0.8 is the average respiratory quotient. At sea level and in a patient breathing room air, the alveolar gas equation may be simplified to:

$$PAO_2 = 150 - PaCO_2$$

This equation neglects the small correction afforded by the respiratory quotient, but is extremely useful for rapidly calculating the A-a DO_2 in clinical situations. (Besides, the respiratory quotient is diet-dependent, so that 0.8 is only a rough estimate any way.)

The A-a DO_2 is simply calculated by subtacting the PaO_2 from the PAO_2:

$$A\text{-}aDO_2 = [FiO_2(P_B - 47) - PCO_2/0.8] - PaO_2$$

The normal A-a DO_2 is 10-15 mmHg, and although it increases with age it is rarely greater than 25mmHg. The A-a DO_2 will be increased by any process that worsens O_2 exchange in the lungs, or by an increase in FiO_2, and thus is a sensitive index of alveolar capillary unit function.

The A-a DO_2 is especially useful clinically when the PaO_2 appears deceptively normal or in patients with chronic hypoxia. For example, a PaO_2 of 75mmHg might suggest adequate O_2 exchange, but if the $PaCO_2$ is 20mmHg a marked A-a DO_2 of 50mmHg exists. An increase in the A-a DO_2 in patients with known lung disease indicates worsening O_2 exchange.

Hypoxemia

Hypoxemia may occur by five distinct mechanisms:

1. Hypoventilation
2. Diffusion impairment
3. Ventilation - perfusion inequality
4. Shunt
5. Decreased inspired oxygen tension

Of these five mechanisms, hypoventilation, ventilation-perfusion (V/Q) inequality and shunt account for most cases.

Central hypoventilation occurs as a result of depression of the respiratory center. As a consequence of decreased minute ventilation, the $PACO_2$ rises and PAO_2 falls. Arterial PCO_2 will subsequently rise. The A-a DO_2 in pure alveolar hypoventilation will be normal. This is to be expected as the alveolocapillary unit is undisturbed in pure hypoventilation. An elevation of the A-a DO_2 in this setting should suggest a superimposed disorder such as COPD, pneumonia or congestive failure. Common causes of central hypoventilation include narcotic and barbiturate overdose, brainstem compression, and central sleep apnea. In addition to central hypoventilation, chest wall and neuromuscular disorders may lead to alveolar hypoventilation.

Diffusion impairment implies failure of the pulmonary end capillary blood to equilibrate with alveolar gas. Equilibration occurs normally in one-third of the total time blood spends in contact with alveolar gas. Diffusion impairment is not a clinically important cause of hypoxemia, except perhaps during exercise in patients with interstitial lung disease or at high altitudes.

V/Q inequality (high or low) is the most common cause of hypoxemia. Low V/Q inequality implies that an alveolar unit is normally perfused but underventilated. As a result the $PACO_2$ rises and the PAO_2 falls in that unit. Blood leaving that unit has low O_2 tension and arterial hypoxemia results. Because the overall PAO_2 is normal, or even high because of compensatory hyperventilation, the A-a DO_2 increases. The presence of V/Q inequality may be confirmed by noting the response to 100% oxygen. 100% oxygen results in a marked rise in arterial oxygen content in this situation. Because the alveolar unit receives some ventilation, 100% oxygen will markedly raise PAO_2 even in the underventilated units. Arterial oxygen tension will rise significantly, although the A-a DO_2 will remain elevated (Figure 2).

Figure 2.

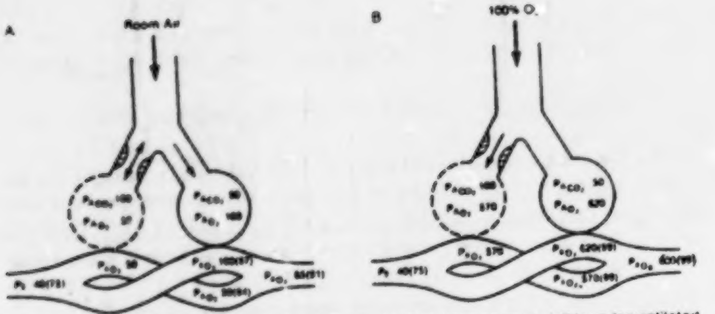

Figure 5.8 The effect of supplemental oxygen on low V/Q: *A*. The unit on the left is underventilated because of an abnormal RC time constant (increased resistance, increased compliance), as a result of this regional hypoventilation there is an increase in alveolar CO₂ ($P_{A_{CO_2}}$), a decrease in alveolar O₂ ($P_{A_{O_2}}$) and a resultant decrease in the arterial oxygen tension of the blood coming from this unit; the neighboring normal unit is normally ventilated; as described in Figure 5.5 the oxygen tension of the systemic blood is derived by averaging the percent saturations. *B*. Despite the diminished ventilation to the unit on the right, ventilation with 100% oxygen will normally wash in oxygen increasing the alveolar oxygen tension of this low V/Q unit; as a result the blood coming from each unit is essentially fully saturated; the percent saturation and oxygen tension of the systemic blood are essentially normal.

Intrapulmonary shunt (right to left) occurs when pulmonary capillary blood perfuses alveolar units that receive no ventilation. PAO_2 for that alveolar unit is identical to mixed-venous PO_2, and pulmonary capillary blood leaving that unit produces arterial hypoxemia. Shunt may be clinically defined by the lack of response to 100% oxygen. The alveolar unit in shunt receives no ventilation, and therefore the PAO_2 of that unit remains at mixed-venous levels regardless of FIO_2. The A-a DO_2 in shunt is elevated and increases further as FIO_2 is increased to 100%. Adult respiratory distress syndrome, pulmonary arterio-venous malformations, and severe pneumonias are common causes of shunt.

Decreased inspired oxygen content normally occurs only at altitude. The FIO_2 is still 0.21 but barometric pressure is diminished. Since the integrity of the alveolar unit is intact, the A-a DO_2 will be normal in the absence of intrinsic lung disease.

VENTILATION ABNORMALITIES

The $PaCO_2$ is a useful index of the adequacy of the ventilatory response. Hypercapnia (increased $PaCO_2$) implies alveolar hypoventilation with an elevation of $PACO_2$. Hypocapnia (decreased $PaCO_2$) implies alveolar hyperventilation, and therefore a depressed $PACO_2$. The relation between alveolar ventilation (VA) and $PACO_2$ is succinctly defined:

$$V_A = \frac{VCO_2}{PaCO_2} \times K \text{ or } PaCO_2 = \frac{VCO_2}{V_A} \times K$$

where VCO_2 equals CO_2 production. Thus we see that $PaCO_2$ is determined by alveolar ventilation and CO_2 production.

Hypercapnia (Alveolar hypoventilation)

Hypercapnia ($PaCO_2 > 43$ mmHg) may occur in association with decreased or with increased minute ventilation (TV x RR). Decreases in minute (and alveolar) ventilation occur with central nervous system depression and with neuromuscular disease. Hypercapnia with an increased minute ventilation occurs with increased dead space due to regional V/Q imbalance (high V/Q), or with an elevated dead space to tidal volume ratio due to shallow rapid breathing. Asthma, chronic bronchitis, and emphysema, when severe, may demonstrate hypercapnia despite an increased minute ventilation.

Occasionally hypercapnia may be precipitated or aggravated by increased CO_2 production. Excessive carbohydrate loads in patients receiving intensive nutrition (nearly always those with severe COPD) have produced this complication.

Hypocapnia (Alveolar hyperventilation)

Hypocapnia ($PACO_2 < 37$mmHg) is the result of alveolar hyperventilation and may be seen with anxiety, drugs (aminophylline, amphetamine or salicylates), CNS infections, acidosis, hypoxemia and in restrictive lung disease.

ACID-BASE BALANCE

The assessment of acid-base balance is an integral part of blood gas analysis. Proper interpretation of acid-base balance requires an understanding of the body's buffer system, and of the anion gap.

The body is able to maintain arterial pH within a narrow range of 7.35-7.45 by virtue of several buffer systems. A buffer minimizes changes in pH by donating or accepting hydrogen ion in response to addition of base or acid, respectively, to the system. The most important blood buffer system is the bicarbonate/carbonic acid buffer pair. Other important buffers are phosphate, and proteins (including hemoglobin). The bicarbonate system is defined by:

$$H_2O + CO_2 \longleftrightarrow H_2CO_3 \longleftrightarrow H^+ + HCO_3^-$$

As seen earlier in this chapter, blood CO_2 content is determined by alveolar ventilation. For practical purposes, HCO_3 concentration is determined by renal mechanisms, or by the addition of fixed acids to the blood.

Checking arterial blood gas accuracy

To avoid wasting valuable time, the first step in arterial blood gas analysis should always be a check of internal consistency. Is the reported HCO_3 derived compatible with the directly measured pH and $PACO_2$? A derivation of the Henderson-Hasselbach equation (equation 1) provides a clinically very useful equation (equation 2):

Equation 1 $$pH = pK + \log \frac{HCO3^{-}]}{[H_2CO_3]}$$

Equation 2 $$[H+] = 24 \times \frac{PaCO_2}{HCO_3^{-}}$$

Equation 2 allows the clinician to check the accuracy of the reported HCO_3 based on the measured pH and $PaCO_2$ and also defines the relationship between [H+], $PaCO_2$ and HCO_3. The latter is essential in approaching clinical acid-base problems.

To effectively use equation 2, the clinician must be able to convert pH to hydrogen ion concentration [H+]. This is easily done using the following rules:

Rule 1 pH of 7.4 = [H+] of 40 nEq/L

Rule 2 Between the pH range of 7.1 and 7.5 the relation between pH and [H+] is approximately linear with 0.01 pH units equivalent to 1 nEq/L. (Figure 3)

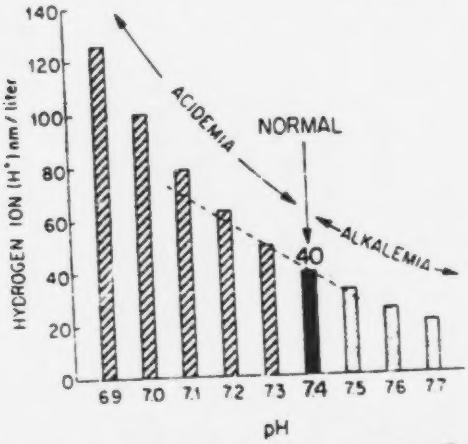

FIG. 3 Relationship of pH to hydrogen concentration. Broken line is drawn to emphasize the (approximately) linear relationship between hydrogen ion concentration and pH over the pH range of 7.1-7.5.

Using rules 1 and 2 we may calculate [H+] over the range of pH most commonly encountered clinically, for example:

	pH	7.1	7.2	7.3	7.4	7.5
"Linear"	[H+]	70	60	50	40	30
Measured	[H+]	79	63	50	40	32

Definitions

Certain basic concepts are fundamental in assessing acid-base balance:

1. Metabolic disorders are defined by primary disturbances of blood HCO_3.

2. Respiratory disorders are defined by primary disturbances of blood $PaCO_2$.

3. Compensatory responses are the anticipated changes in $PaCO_2$ or HCO_3 which occur in response to a primary metabolic or respiratory disorder. Compensatory responses attempt to maintain pH in the normal range of 7.35-7.45, and never cause an over correction.

4. Acidemia defines the presence of sufficient excess H+ ion to produce an acid pH (<7.35).

5. Acidosis refers to the metabolic or respiratory process generating excess H+ ion. Acidosis may be present without an accompanying acidemia.

6. Alkalemia defines a decrease in H+ ion sufficient to produce an alkaline pH (> 7.45).

7. Alkalosis refers to the metabolic or respiratory process responsible for the H+ ion deficiency. Alkalosis may be present without an accompanying alkalemia.

8. Simple acid-base disorders are due to an isolated disturbance of blood HCO_3 or $PaCO_2$ in association with an appropriate compensatory response.

9. Mixed acid-base disorders are due to a combination of primary disturbances of blood HCO_3 and $PaCO_2$. A mixed disorder is suspected when the measured $PaCO_2$ and HCO_3 are not consistent with the calculated compensatory $PaCO_2$ and HCO_3 for a simple acid-base disorder.

Anion Gap

A powerful tool in the assessment of acid-base balance is the anion gap. The law of electroneutrality dictates that anions must equal cations in the blood. The anion gap is calculated as the sodium concentration minus the chloride and bicarbonate concentrations:

$$AG = Na+ - (HCO_3^- + Cl^-)$$

The anion gap represents unmeasured anions such as proteins, sulfates, phosphates, and organic acids. The anion gap is normally 8-12 (mean 10) in mEq/L. An elevated anion gap may be seen in metabolic acidosis, administration of the sodium salts of lactate, citrate, and acetate, carbenicillin therapy, and mild (2-3 mEq/L) increases with dehydration and alkalosis.

Metabolic Acidosis

Metabolic acidosis is defined by a primary disorder of blood HCO_3 resulting in a decrease in serum HCO_3 concentration. As a consequence of metabolic acidosis minute ventilation increases, and a compensatory decrease in $PaCO_2$ results. From equation 2 we realize this offsets the pH change caused by a decrease in HCO_3. The expected compensatory $PaCO_2$ decrease may be calculated as follows:

$$PaCO_2 = 1.5\,(HCO_3) + 8 \pm 2$$

If the measured $PaCO_2$ is higher than predicted, respiratory acidosis is also present. If the measured $PaCO_2$ is lower than predicted, respiratory alkalosis is also present.

The anion gap is useful to categorize metabolic acidosis, and formulate an appropriate differential diagnosis. Metabolic acidosis is conveniently divided into "high anion gap acidosis" and "normal anion gap acidosis"

High Anion Gap

Methanol ingestion
Uremia
Diabetic ketoacidosis
Paraldehyde
Infections (lactic acidosis)
Ethylene glycol ingestion
Salicylate ingestion

Normal Anion Gap

Ureteral diversions
Saline
Early renal failure
Diarrhea
Carbonic anhydrase inhibitors
Amino acid infusions
Renal tubular acidosis
Hyperparathyroidism
Triamterene
Spironolactone
DKA (post treatment)

A useful concept is that in metabolic acidosis for every increase (or decrease) of 1 mEq/L in the anion gap above (or below) 10 mEq/L, the blood HCO_3 will decrease (or increase) by 1 mEq/L. Thus, we can predict in a metabolic acidosis the expected HCO_3 for a given anion gap. For example, in a patient with sepsis and an anion gap of 20 mEq/L, we would expect the blood HCO_3 to decrease by 10 mEq/L from a normal value of 25 mEq/L. We would predict a HCO_3 of 15 mEq/L. If the measured HCO_3 is for example 20 mEq/L we immediately know there is a concomitant metabolic alkalosis.

Metabolic Alkalosis

Metabolic alkalosis is defined by a primary disturbance of blood HCO_3 resulting in an increase in serum HCO_3 concentration. As a consequence of metabolic alkalosis minute ventilation decreases and a compensatory increase in $PaCO_2$ results. The expected $PaCO_2$ increase may be predicted:

$$PaCO_2 = 0.9\ (HCO_3) + 9$$

If the measured $PaCO_2$ is greater than expected, respiratory acidosis is also present. If the measured $PaCO_2$ is lower than expected, then respiratory alkalosis is also present.

Metabolic alkalosis is conveniently divided into chloride responsive and chloride unresponsive types. Normal saline infusions will correct chloride responsive metabolic alkalosis.

Chloride Responsive

Vomiting
Nasogastric suction
Chloride-wasting diarrhea
Villous adenoma
Diuretic therapy
Post-hypercapnia
Carbenicillin or Penicillin

Chloride Unresponsive

Hyperaldosteronism
Cushings Syndrome
Gluco- or mineralocorticoid therapy
Bartter syndrome
Alkali ingestion

Respiratory Acidosis

Respiratory acidosis is defined by a decrease in alveolar ventilation, resulting in an increase in $PaCO_2$. As a consequence of acidosis the kidney will eliminate H+ ion and retain HCO_3. The renal response is not complete for 24 hours, and the expected compensatory HCO_3 increase varies for the acute and chronic setting:

Acute Respiratory Acidosis

HCO_3 increases 1 mEq/L for every
10mm Hg increase in $PaCO_2$

Chronic Respiratory Acidosis

HCO_3 increases 3.5 mEq/L for every
10mm Hg increase in $PaCO_2$

If the measured HCO_3 is lower than expected, metabolic acidosis is also present. If the measured HCO_3 is higher than expected, then metabolic alkalosis is also present.

Respiratory acidosis may be divided into disorders causing decreased minute ventilation, and disorders producing V/Q inequality, or increased physiologic or end time dead space.

Decreased Minute Ventilation

CNS depression
Neuromuscular disease
  - myopathy
  - neuropathy
Thoracic cage limitation
  - Scoliosis
  - Scleroderma
  - Crush injury
Impaired lung motion
  - pleural effusion
  - pneumothorax

V/Q Inequality

Aspiration
Tumor
Bronchospasm
Laryngospasm
COPD
Severe Pneumonia
Severe CHF

Respiratory Alkalosis

Respiratory alkalosis is defined by an increase in alveolar ventilation resulting in a decrease in $PaCO_2$. As a consequence of alkalosis, the kidney will retain H+ ion and excrete HCO_3. Again the renal response is not complete for 24 hours, and the expected compensatory decrease in HCO_3 varies for the acute and chronic setting.

Acute Respiratory Alkalosis

HCO_3 decreases 2 mEq/L for every
10mm Hg decrease in $PaCO_2$

Chronic Respiratory Alklaosis

HCO_3 decreases 5 mEq/L for every
10mm Hg decrease in $PaCO_2$

If the measured HCO_3 is lower than expected metabolic acidosis is also present. If the measured HCO_3 is higher than expected, then metabolic alkalosis is also present.

Respiratory alkalosis occurs secondary to alveolar hyperventilation. The differential diagnosis is as follows:

Anxiety
CNS disorders
  - CVA
  - Tumor
  - Infection
Drugs
  - Salicylate
  - Catecholamines
  - Progesterone
  - Analeptics

Fever, sepsis
Hyperthyroidism
Hypoxia
Mechanical ventilation
Pregnancy
Cirrhosis
Mild CHF
Lung disease (generally associated with hypoxia)
  - Interstital
  - Pneumonia
  - Pulmonary embolus

In this section I have defined the relation between pH, $PaCO_2$ and HCO_3 in determining acid-base balance. I have defined simple and mixed acid-base disorders, and shown how they may be identified by predicting the compensatory response. Finally, I have shown the utility of the anion gap in acid-base assessment. In dealing with clinical acid base problems, I recommend the following approach:

1. Check the internal consistency of the ABG's using equation 2.

2. Look at the pH. Is acidemia or alkalemia present?

3. Calculate the anion gap.

4. Use the clinical history, physical exam, $PaCO_2$ and HCO_3 to determine the primary disorder.

5. Look at the measured $PaCO_2$, HCO_3 and anion gap to assess if a simple or mixed disorder is present, after calculating the compensatory response.

6. Finally use available nomograms for difficult to categorize diseases (Figure 4).

Figure 4

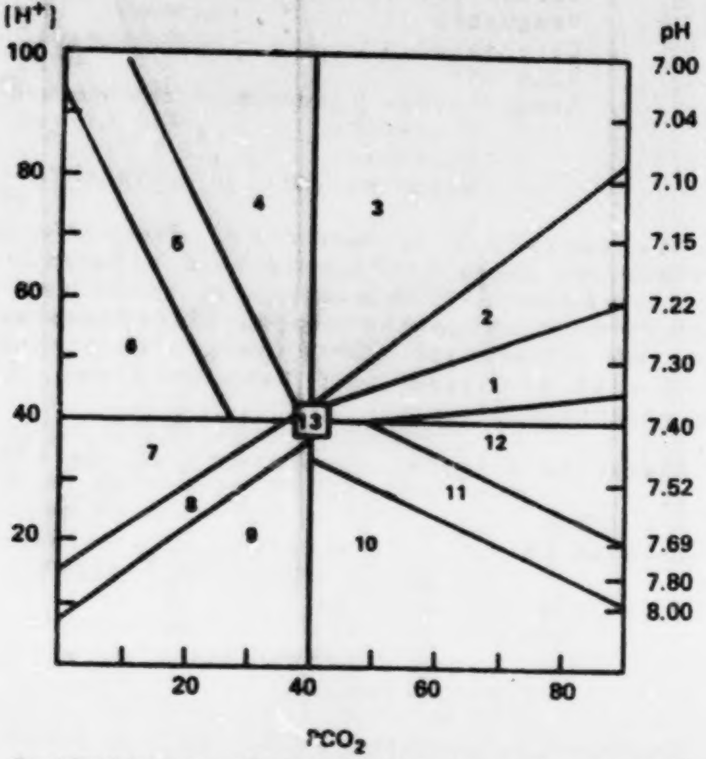

Figure 4 Quadrant diagram showing relationship between Pa_{CO_2}, pH, and H^+. Thirteen quadrants are identified presenting the 95% confidence limits of these acid-base disturbances: *1)* chronic respiratory acidosis with renal compensation; *2)* acute respiratory acidosis; *3)* combined respiratory and metabolic acidosis; *4)* metabolic acidosis without compensation; *5)* compensated metabolic acidosis; *6)* mixed metabolic acidosis and respiratory alkalosis; *7)* maximally compensated respiratory alkalosis; *8)* respiratory alkalosis; *9)* combined respiratory and metabolic alkalosis; *10)* poorly compensated metabolic alkalosis; *11)* normally compensated metabolic alkalosis; *12)* mixed metabolic and respiratory acidosis; *13)* normal acid-base status (adapted from McCurdy (15)).

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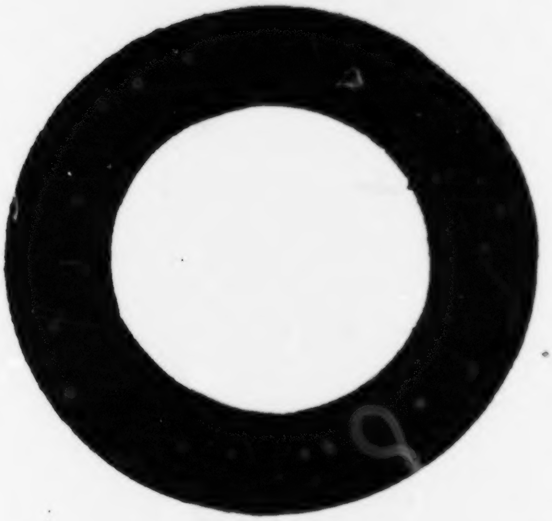


BRONCHOSCOPY

Lawrence R. Schacht, Lieutenant Colonel, USAF, MC

INTRODUCTION

Direct visualization of the lung's bronchial airways is indispensable for diagnosis and management of thoracic diseases. For many years the open-tube rigid bronchoscope has been used in the operating room; local anesthesia is sometimes employed, but the procedure is more pleasant for a patient if performed under general anesthesia. The flexible fiberoptic bronchoscope (FBB) developed in Japan has altered the practice of respiratory medicine since its introduction to clinical use in 1967. The low incidence of complications, better patient acceptance with only topical anesthesia, lower cost and operating personnel requirement, with greater visualization of the bronchial tree all have assured its worldwide acceptance. (8)

FFB is now the initial operative procedure of choice for diagnosing most indeterminate chest lesions, including patients with normal chest x-rays who have hemoptysis (11) or abnormal sputum cytology.(12) Endoscopically visible bronchial lesions are biopsied directly, while peripheral densities are sampled under fluoroscopic guidance, and mediastinal or parabronchial masses after CT localization. FFB plays a vital therapeutic role in airway management by assessment of airway patency, removal of retained secretions or mucus plugs.

Rigid bronchoscopy, with its ability to assure an open airway, better provide supplemental oxygenation and even ventilatory assistance, is still preferred for management of major hemorrhage, some tumors or foreign bodies of central airways, and if the trachea is small-such as normally occurs in infants and children, or abnormally occurs in adults with laryngeal or tracheal pathology.(8)

TECHNIQUE

Open-tube rigid bronchoscopy (Figure 1) will not be further discussed. FFB is performed in a supine or sitting patient by either oral or transnasal approach (Figure 2) or even through the rigid bronchoscope.

Figure 1

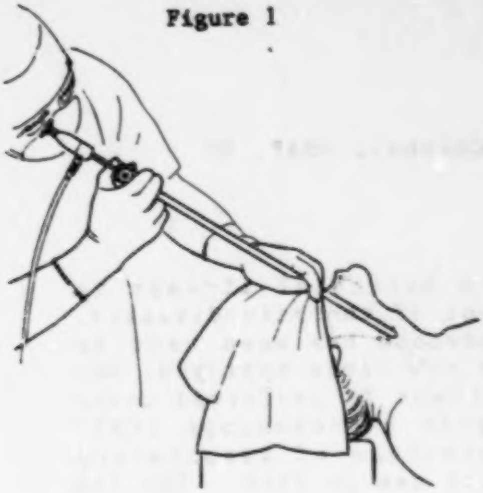
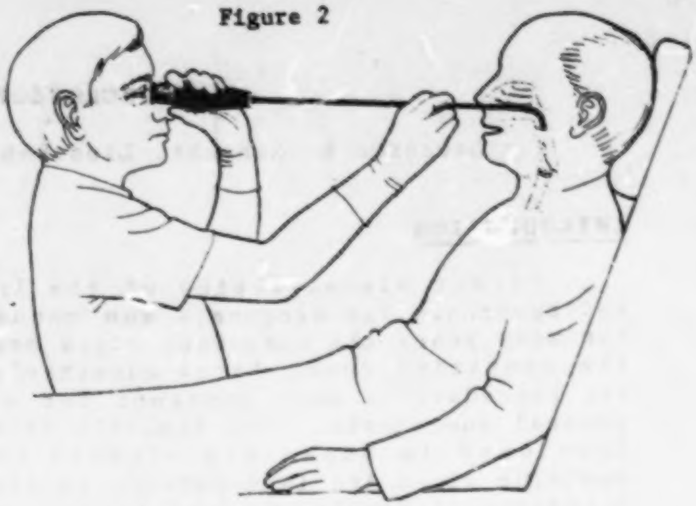


Figure 2



FBB instruments range from 2.7 to 6.5 mm in outside diameter. The utility of the larger scopes owes to an inner channel for instillation or suction of liquids, passage of biopsy forceps, brushes, needles, etc. The narrow aspirating channel does not establish an airway and is too small to handle flooding of blood or purulent material, however, so FFB through an 8.0-9.5 mm oral endotracheal tube (often guiding it over the preinserted FFB) is preferred for selected patients.(5) Patients with tracheostomies or on mechanical ventilators even with positive pressure can be examined. Every patient is monitored on a cardioscope and has IV access. Significant falls in PaO2 occur frequently during FFB especially with suctioning, coughing or lung lavage.(6) Continuous fingertip or other transcutaneous oxyhemoglobin monitors are convenient. Supplemental oxygen for all patients is the best technique to avoid adverse consequences such as arrhythmias.(7)

FFB usually is done as a clean or semi-sterile procedure.(5) Any cleaning and disinfection of instruments adequate to kill bacteria and Hepatitis B virus also prevents spread of Mycobacteria or HIV. Gloves, mask, gown and eye protection should be worn as for any procedure with the possibility of exposure to blood or splattered body fluids.(15) SBE antibiotic prophylaxis should be considered for patients with predisposing cardiac conditions.

Premedication of the fasting patient with atropine blocks the vasovagal reflex, reduces obscuring secretions and reactive bronchospasm. A sedative (e.g., Vistaril, Phenergan) and a narcotic antitussive are often given. After predmication, lidocaine is the preferred topical anesthetic, first in the oral or nasopharynx and then, as the scope advances, on vocal cords and airways while systematic exam of the bronchi in both lungs is carried out.

PATIENT SCREENING PRECAUTIONS

History and physical should focus on any cardiac ischemia or arrhythmia, pulmonary disease (especially asthma, pulmonary hypertension, hemoptysis), immunoincompetence, medications (e.g. Coumadin) and drug allergies since these represent high risk situations. Routine lab studies include chest x-ray, CBC, BUN, and (for biopsy) PT, PTT, platelet count and sometimes bleeding time. ECG, ABG and spirometry are indicated for most hospitalized or high risk patients. Absolute contraindications for FBB are an uncooperative/unconsenting patient, and operator inexperience. Other dangerous situations require careful weighing of risks and benefits:

1. Potentially unstable cervical spine (e.g. trauma, spondylitis).

2. Uncontrolled bronchospasm (delaying FFB for maximal bronchodilator therapy may be prudent; risks of FFB in milder asthma may have been overstated).(15)

3. Respiratory insufficiency - PaO2 $<$ 60-65 despite supplemental O2, or PaCO2 $>$ 45. (6)

4. Recent myocardial infarction (within 6 weeks), uncontrolled arrythmia or severe congestive heart failure.(8)

5. Active, untreated pulmonary tuberculosis (for its threat to medical personnel).

6. Additional threats specifically for transbronchial lung biopsy include:

   a. Uremia or any uncontrolled bleeding diathesis. (Pre-procedure platelet/FFP transfusions can help but serious complications are still more frequent, as Papin reports. (13)

   b. Mechanical ventilation.(14)

   c. Pulmonary hypertension.(8)

Pediatric Note: The need for ventilation around rather than through the instrument previously limited FFB in young children. New directable, ultra thin scopes now make FFB well tolerated even in infants considered too small to undergo rigid bronchoscopy. Fan reports on a large series of pediatric patients with diagnostic information obtained in 87% on a variety of airway problems.(16)

COMPLICATIONS

Three large, retrospective surveys (by mail) of 112,500 procedures delineate the risks of FFB to the patient, and are well reviewed by Shure.(17) The most common complications are pneumothorax, laryngobronchospasm and bleeding. Overall morbidity rate has been estimated to be 0.08 to 0.15%, and the mortality 0.01 to 0.04%. The deaths have generally occurred in patients with severe pneumonia, severe COPD, myocardial infarction or advanced cancer. In addition, both morbidity and mortality increase with the use of transbronchial biopsy. In the most recent series (40,000 procedures), transbronchial biopsy was associated with a morbidity rate of 2.7% compared to 0.12% without biopsy; mortality was 0.12% with biopsy and 0.04% without. The nature of voluntary reporting used in those three series probably understates the incidence of serious complications. In another prospective series of nearly 1,000 FFB procedures from multiple hospitals, serious morbidity occurred in 1.7% and mortality was 0.1%.(18) Summarizing information from multiple studies about specific complications:

1. Pneumothorax. Related to less than 1% of bronchial brush biopsies, and 1 to 5% of transbronchial biopsy procedures. Most require no treatment. Fluoroscopy during biopsy clearly reduces incidence (from 2.9% to 1.8% in one series).(19) Only one lung is biopsied. Afterward, fluoroscopic check for pneumothorax is mandatory; a chest x-ray may also be done. Significant late pneumothorax almost never occurs, and numerous authors report performing outpatient biopsies on responsible patients who are sent home after 1-3 hours observation and told of late symptoms to self-monitor.(20)

2. Anesthetic reaction. Combines with hypoxemia, other premedications, anxiety and autonomic stimulation to increase risk of significant arrhythmias. Reactions to tetracaine in one series are much higher than with lidocaine topical anesthetic.

3. Bleeding. Hemoptysis occurs in up to 9% of non-high risk transbronchial lung biopsy patients, almost always mild and self-limited; increased in immunocompromised patients (15%) and uremics (45%).(8) Not an excessive risk in diagnostic FFB of patients who present with hemoptysis, even within the first 48 hours.(21) Despite inadvertent aspiration of major vascular structures, only a single case of significant bleeding has been described complicating transbronchial needle aspiration of mediastinal lymph nodes. A spontaneously resolving hemomediastinum, without clinical deterioration, occurred in a patient with no evidence of bleeding diathesis. (29).

4. Fever. Shown in several series to occur in up to 16% of patients.(17,18,22) Some developing fever after FFB have an obvious pre-existing cause (e.g. obstructing tumor). In the remaining patients fever occurs more commonly as a self-limited complication of the FFB procedure, and may be more frequent after lavage (up to 26%).(26) Bacteremia from FFB, even with transbronchial needle aspiration, is exceedingly rare.(22) New pneumonia requiring antibiotics occurred after 0.5% of procedures

in one series,(18) while fever without infection was reported at 1.2% and 6% rates.(18,22)

DIAGNOSTIC INDICATIONS AND METHODS:

A. *Lung Cancer*-primary or metastatic.

Clearly the most common reason to recommend FFB. A sampling of indicators that could raise this concern even with a normal chest x-ray include: hemoptysis, cough, vocal cord dysfunction, localized wheeze, abnormal sputum cytology. Also possible spread or synchronous tumors in a patient with another known malignancy (e.g. FFB in patients with esophogeal or head and neck cancer to plan their therapy(27), so-called "triple endoscopy").

1. Diagnosis. Zavala's original series of 600 patients included 330 with bronchogenic carcinoma, and FFB made the tissue diagnosis in 279 (85%).(1) His even higher yield (94%) when tumor mass was visible through the scope is also typical; bronchial brushing, washing or needle aspiration of these visible masses adds nothing to the direct forceps biopsy except for occasional tracheal or mainstem lesions located where the forceps slip off. When the central endobronchial tumor involvement is submucosal or peribronchial (constricting or invading) then using all methods does increase the diagnostic yield to 97%, compared to 55% with forceps biopsy alone.(17) In another series, Schenk improved the overall diagnostic rate of FFB from 64% to 71% for these central bronchogenic tumors without discreet airway mass by using transbronchial needle aspiration (TBNA) after localizing the lesions from CT scan.(2) For peripheral masses on chest x-ray but not visible in an airway, transbronchial biopsy with brushing (under fluoroscopy to improve yield and reduce pneumothorax risk) was still diagnostic in 71% of Zavala's patients. Adding transbronchial needle aspiration for peripheral masses may improve diagnostic rate.(31) For peripheral lesions 2cm or smaller FFB yield is poor in all series, and transthoracic needle aspiration is usually the next or even initial procedure. In occult lung cancer (positive sputum cytology, negative x-ray, and negative exam of upper airways and mouth) most tumors are squamous, and 60 to 70% will be found in central airways with the first FFB, the rest detected on repeat exams for up to 3 years.(12) Metastatic cancer within the lung is approached by FFB in the same way as primary tumor, and takes three presentations: 1) endobronchial mass - most often from melanoma, breast, GU tract, with greater than 90% biopsy diagnosis; 2) peripheral nodules - transbronchial biopsy yield usually less than 50%, said to be because hematogenous mets don't communicate with airways as well(31); 3) lymphangitic infiltrates - with greater than 90% transbronchial biopsy diagnosis rate.

2. Staging. Remember, nearly every patient with bronchogenic carcinoma when initially diagnosed needs FFB because 9 to 15% have multicentric (synchronous) tumors, sometimes in different lobes.(12) FFB appearance of a tumor may show

unresectability (e.g. bronchial involvement less than 2cm from carina). Also, various biopsies can prove unresectability. Forceps mucosal biopsy of a visually-abnormal main carina always should be done because occasionally tumor can spread from a mainstem or lobar endobronchial site to the carinal mucosa or submucosa, and transcarinal needle aspiration still be negative.(30)

The safety, ease and yield of mediastinal sampling by TBNA is well established for carinal and paratracheal biopsy.(2,17,22,30,32) Puncture of airway wall or carina with aspirating 20ga to 23ga needles or the newer 18ga needles capable of tissue coring has caused no mortality and much lower morbidity than transbronchial lung biopsy. It requires expert cytopathology support. TBNA saves a significant number of patients from surgical staging to discover unresectable tumors. Shure reports 15% of three-point carina aspirates positive (16/110) by doing all patients routinely(30); sensitivity rate was not assessed in her study. Using CT scans to direct TBNA to the carina and other paratracheal sites of enlarged nodes, Wang(32) and Schenk(33) found mediastinal tumor in 44% (17/39) and 19% (17/88) of all their patients, respectively, being staged for bronchogenic carcinoma. Sensitivity of TBNA in the two series was 71% (17/24) and 50% (17/35), respectively. Both authors argue for the value of CT scan pre-FFB to detect occasional patients with unsuspected contralateral or pretracheal sites of mediastinal node involvement. CT may also detect unsuspected liver or adrenal tumor spread, or help later radiation planning, etc. The very low rate of false-positive mediastinal TBNA (2/472, by pooling three series) is reassuring since no patient should be denied potentially curative surgery. For the same reason, enlarged mediastinal lymph nodes by CT scan still require tissue confirmation.

B. Pulmonary infections

1. Bacterial. Cultures of the lung through an FFB that has traversed the contaminated oral pharynx can sometimes be meaningful using a protected specimen brush contained in its own sterile plastic catheter.(23) However, this is controversial and many reports show high false positive and false negative rates, particularly in the presence of multiple infections.(17) Injecting topical anesthetic into the tracheobronchial airways before the sampling also increases contamination, and quantitative culturing of the specimen is essential. In critically-ill patients the tracheobronchial airways are rapidly colonized by potential pathogens, so the protected brush catheter sample from a pneumonia in such patients may help determine which of the organisms from the central airways are responsible for the infection.(24) Bartlett emphasizes that bacterial infections of the lung contain 100,000 or more bacteria/ml of exudate or gram tissue. Lower concentrations from any specimen source must be interpreted cautiously. Also, saliva contains normal flora species exceeding that cutoff of "significance" by 100-1000x.(23)

2. Tuberculous and Fungal Infections. FFB is particularly important when these infections occur in immunocompromised patients, and in the diagnosis of sputum smear-negative tuberculosis. Lung brushings and biopsies can provide an immediate diagnosis by staining of the specimens in up to 50% of tuberculosis cases, with additional later positive cultures.(17) Fungal infections can be more difficult to detect, but stains and culture of FFB brushing and biopsy specimens improve diagnosis of histoplasmosis, coccidioidomycosis, cryptococcosis, and both allergic bronchopulmonary and invasive aspergillosis. (Remember, aspergillus can be a normal colonizer of upper airways)

3. Immunocompromised Hosts. Diagnostic yield of FFB in immunosuppressed patients with diffuse infiltrates varies by author from [illegible]% to nearly 100%.(7,25) Problems interpreting protected catheter brush cultures for bacterial pneumonias were already discussed. The highest diagnostic yield from FFB is in patients likely to have opportunistic infections (e.g. Legionella, Pneumocystis). It is considerably less in patients who have received chemotherapy or some transplants and are likely to have a variety of drug or radiation related changes, fibrosis, or graft-host reactions. Transbronchial biopsies, lung brushings and segmental bronchoalveolar lavage (BAL) can all be used, but washings of the proximal bronchi through the FFB are seldom helpful. Highest yields in opportunistic infection are obtained with a combination of BAL and biopsy, but at least in AIDS BAL alone is almost as effective.(17,36) If an individual patient can tolerate FFB and infection is a consideration, then FFB is an appropriate initial procedure. Both biopsy/brushing and BAL can be done if no bleeding disorder is present, but lavage alone may be safest in thrombocytopenic or ventilator patients.(13,14) If risk of bleeding is too high or immediate diagnosis is needed in a patient unable to tolerate two procedures then open lung biopsy may be more appropriate. In every case, the critical importance of advance coordination with the microbiology and histopathology labs to assure proper specimen handling cannot be overemphasized. When this is done, numerous authors emphasize the high rate of specific diagnoses obtained same-day or next-day in these patients.

The BAL procedure itself merits comment, and I draw from Turner-Warwick's recent review.(26) BAL was first done in the 1960's occasionallly as a large volume therapy to remove excessive secretions in severe asthma or bronchiectasis, then in the 1970's via the FFB as small volume segmental lavage primarily for research on interstitial lung diseases. Claims for its clinical value were, until recently, controversial; but its low risk to the patient is not. By wedging the FFB tip in a peripheral small bronchus, alternately instilling then aspirating 20 ml to 50 ml aliquots of saline up to a total injected volume of 100 ml to 300 ml, approximately 50% of the fluid is recovered for studies. These include total and differential cell counts, special appearances of cells, chemistry and special analyses of the supernatant, and stains and cultures for bacteria, fungi, viruses and protozoa. Complications include transient decreases in vital capacity and/or peak expiratory flow (by greater than 20% in one quarter of patients, but rarely requiring dilator therapy); fever in about one quarter of patients; but no ABG decrement unless lavage volumes exceed one liter. Nasal oxygen is routinely administered to all patients during and for two hours post-procedure, and all changes resolve within 24 hours. (17,26)

C. Hemoptysis

The major question is a clinical judgement of which patients should have FB and when. Low-grade hemoptysis longer than a week in a person over 40 with lung cancer risks - probably yes. Mild hemoptysis in a young patient with acute bronchitis - probably no. But those are the easy ones! Fear of aggravating bleeding by diagnostic FFB is unfounded. Smiddy localized bleeding to the subsegmental level by FFB in 93% (66/71 patients).(21) Other series reporting on patients with normal chest x-rays do not approach that rate of localization. (11,34) Discovery of specific cause is fairly frequent, and in a group of 55 patients with hemoptysis and normal chest x-rays, Zavala found these diagnoses(1):

32 - normal, no further bleeding
9 - endobronchial cancer

8 - bronchitis

3 - mitral stenosis
3 - cancer of larynx or nasopharynx

A literature summary of 534 patients with normal chest x-rays and hemoptysis showed 3% cancer incidence (16 patients).(34) An abnormal chest x-ray greatly increases risks of cancer, or course, but patients with a chest x-ray abnormality are sometimes found to be bleeding from a different site.

Hemoptysis with pulmonary hemorrhage (more than 600ml blood over 12-24 hours) is a medical-surgical emergency, requires hospitalization, and rigid bronchoscopy is usually preferred over FFB for localizing and managing bleeding (although either instrument can help place a balloon catheter to tamponade or occlude a bleeding bronchus).(17) Pulmonary hemorrhage in immunocompromised patients can be diagnosed by bronchoalveolar lavage (BAL) by finding hemosiderin-laden macrophages on cytology.(4,26,37)

D. Interstitial lung disease.

The role of FFB in diagnosis of noninfectious, nonmalignant diffuse interstitial disease is controversial. The single exception is sarcoidosis, in which transbronchial biopsy of radiographically normal or abnormal lung yields granulomas in 90% of patients (visibly abnormal bronchial mucosa also should be biopsied).(3) Sporadic other rare diagnoses can be made by these tiny biopsies e.g. lipid pneumonia, pulmonary alveolar proteinosis, but surgical open lung biopsy is preferred for most interstitial pneumonitis. BAL can occasionally diagnose eosinophilic granuloma, inorganic dust disease like asbestosis, or a pulmonary lymphoma or other interstitial neoplasm. Much is written on BAL for diagnosis or monitoring treatment of sarcoidosis, other immunologically-mediated fibrotic lung diseases, or even lymphocytes in HIV disease; but its value for these is limited to those research centers which work intensively with this procedure. Even Turner-Warwick acknowledges selecting "an open lung biopsy when the changes are likely to be less specific and when 'staging' of the disease is important for therapeutic reasons".(26)

THERAPEUTIC BRONCHOSCOPY:

FFB is important in airway management during acute respiratory failure, both in assessing patency and in mechanical removal of secretions, occasionally in facilitating a difficult tracheal intubation. Patients on mechanical ventilation can be safely examined using a tracheal tube adapter, but with several caveats:

- Use a large endotracheal tube (at least 8mm).

- Increase FIO to 1.0 or 100% during the procedure.

- Do not stop PEEP or CPAP; reduce PEEP since the presence of the FFB will increase the level of PEEP.

- Raise the pressure limit on the ventilator; otherwise it will "dump" most of the breaths because of the resistance engendered by the bronchoscope.

- Monitor cardioscope, ventilation and continuous O2 saturation closely.

- Keep procedure as short as possible, use short periods of suctioning.

- Topical anesthetic is still important to reduce agitation, arrhythmias.

Atelectasis in ICU patients can be reversed in 80 to 85% of patients and thus even reverse refractory hypoxemia.(8) Direct vision with ability to locally lavage mucus plugs (using saline or occasionally acetylcysteine) and suction is usually effective, and repeated as necessary. Endotracheal tube position, mucosaal condition, TE fistula can all be monitored.

Other indications for therapeutic FFB are limited. Removal of broncholiths or foreign bodies, especially in children, is best done by rigid bronchoscopy.(5) Balloon tamponade of pulmonary hemorrhage was mentioned. Facilitating drainage of lung abscess can be done by passing a forceps or catheter tube with fluoroscopy into the lesion; simultaneous biopsies are often done to rule out cavitated carcinoma.(5) Rarely, this can result in endobronchial spread of purulent material and massive pneumonia. FFB is used occasionally in detection and photo radiation of early bronchogenic carcinoma(9) or Nd-YAG laser resection of benign or malignant tracheobronchial lesions causing bleeding or obstruction.(10) FFB also has been used for brachytherapy, the implantation of local radiation "seeds" in endobronchial or peripheral lung carcinomas for palliation of hemoptysis or airway occluding lesions.(28) FFB can also be used to enhance the value and ease of doing selective contrast bronchograms.(35)

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THORACENTESIS AND PLEURAL BIOPSY

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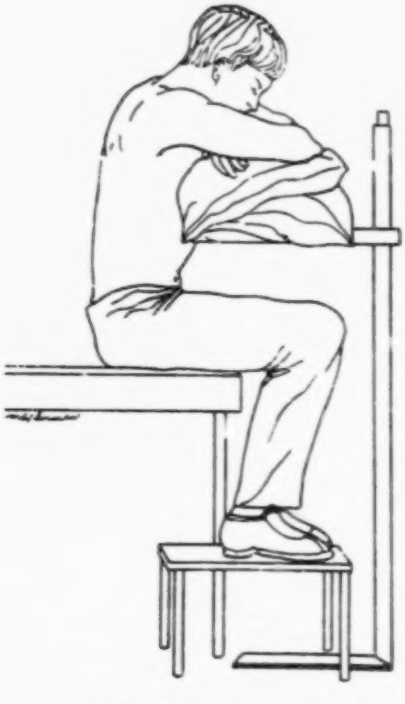
THORACENTESIS

Thoracentesis should be performed in any patient with a pleural effusion in whom the etiology of the effusion is unclear, or when the effusion compromises respiratory function (1). It is recommended that thoracentesis not be performed if the thickness of the fluid in decubitus x-rays is less than 10mm. In this case, the procedure can be performed under ultrasound guidance if clinically indicated. There are few contraindications to thoracentesis, the most common being bleeding diathesis and anticoagulation therapy. When a thoracentesis is needed in an anticoagulated patient or one with a bleeding diathesis, an attempt to normalize coagulation parameters should be made prior to performance of the procedure. When thoracentesis is strongly indicated but the bleeding diathesis cannot be fully corrected or anticoagulation reversed, the procedure can be safely performed using a small needle if the operator is careful. The procedure is usually performed with the ptient seated and leaning slightly forward to maximize the interspace between the ribs, with arms propped up on a suitable support.

Figure 1

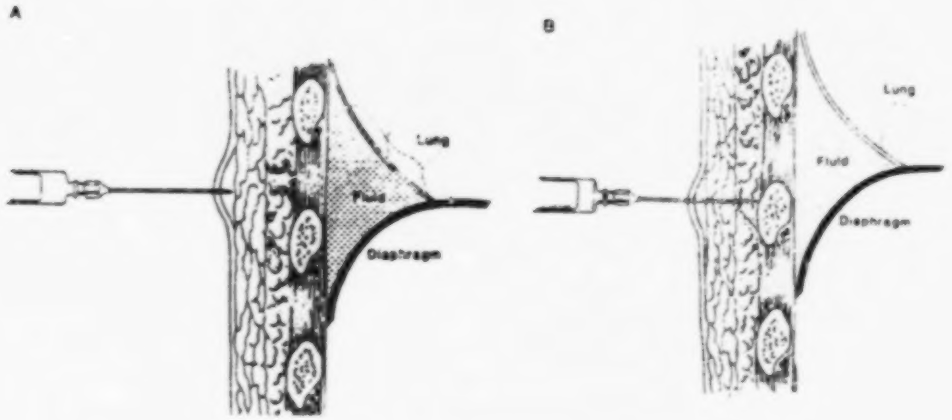


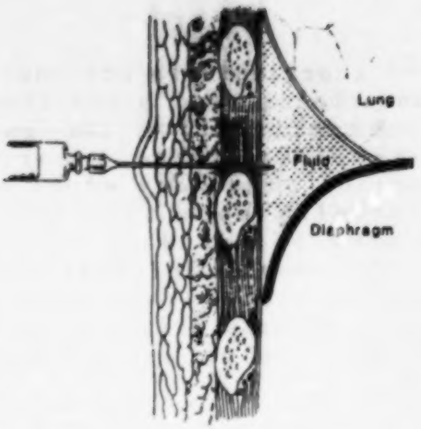
Recommended position of the patient for diagnostic or therapeutic thoracentesis

The effusion is located as an area of dullness to percussion or by tactile fremitus. The hemidiaphragm on the side of the effusion should be approximated by locating the opposite hemidiaphragm, to avoid placing the thoracentesis needle into or below the diaphragm. In the case of a small or loculated effusion, ultrasound (2,3) or fluoroscopy (4) may be helpful in localization for thoracentesis. In such circumstances, it may be necessary for the patient to assume a lateral decubitus position between two beds with the physician performing the thoracentesis from below.

After adequate preparation and local anesthesia, the thoracentesis needle is directed toward the upper one-third of the lower rib in the selected interspace, and the needle is then "walked" over the top of the rib to prevent trauma to the intercostal vessels which run beneath each rib. Great care must be taken to avoid injuring the intercostal vessels, especially in elderly patients, as there is a trend toward increased tortuosity of the intercostal arteries with advancing age (5), decreasing the amount of space for safe insertion of the thoracentesis needle.

Figure 2





Diagnostic thoracentesis. *A*, The skin is injected using a 25-gauge needle with a local anesthetic agent. *B*, The periosteum is injected with the local anesthetic. *C*, The pleural space is entered, and pleural fluid is obtained.

Table 1 illustrates usual equipment required to perform a thoracentesis. Most commercially available thoracentesis kits supply most of these.

Table 1

Materials Needed for Diagnostic Thoracentesis

Basic Materials
- Lidocaine 1 or 2%
- Aqueous Heparin, 1000 U/ml
- Atropine
- Antiseptic solution
- Alcohol swabs
- Sterile gloves
- 6 4 × 4-inch gauze pads
- Sterile drape with center hole
- Sterile drape (to cover bed)
- Adhesive tape
- 2 5- to 10-ml syringes
- 1 50-ml syringe
- 1 No. 25 needle, ⅝ inch long
- 2 No. 20 to No. 22 needles, 1½ inches long
- Bandaids

Additional Materials for Therapeutic Thoracentesis
- 2 No. 14 needles and catheters
- 1 3-way stopcock
- 1 sterile container for pleural fluid
- 1 50-ml syringe (additional)

Additional Materials for Pleural Biopsy
- Pleural biopsy needle
- Scalpel
- Formalin

Complications of thoracentesis are unusual and include local pain, hemorrhage, hemothorax, and pneumothorax. A PA expiratory chest film should be obtained after each thoracentesis to determine if a pneumothorax has occurred. Additionally, unilateral re-expansion pulmonary edema may occur if too much fluid is removed (usually more than two liters) (6). It is thought that this occurs secondary to decreases in pleural pressures produced by removal of fluid from the pleural space. Light et al have demonstrated that this complication can be prevented by monitoring pleural pressure during fluid removal and not allowing it to fall below minus 20cm H_2O (ARRD 121:799, 1980) (See Figure 3).

Figure 3

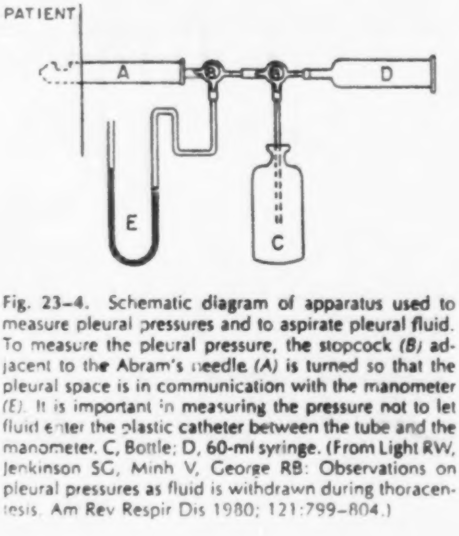


Fig. 23–4. Schematic diagram of apparatus used to measure pleural pressures and to aspirate pleural fluid. To measure the pleural pressure, the stopcock *(B)* adjacent to the Abram's needle *(A)* is turned so that the pleural space is in communication with the manometer *(E)*. It is important in measuring the pressure not to let fluid enter the plastic catheter between the tube and the manometer. C, Bottle; D, 60-ml syringe. (From Light RW, Jenkinson SG, Minh V, George RB: Observations on pleural pressures as fluid is withdrawn during thoracentesis. Am Rev Respir Dis 1980; 121:799–804.)

The recommended studies of pleural fluid are illustrated in Table II. Fluid analyzed for pH should be kept anaerobic and in ice, ideally in the original syringe used to remove it from the pleural space.

Table II

Laboratory Distribution of Pleural Fluid Obtained
with Diagnostic Thoracentesis

Laboratory	Amount (ml)	Test Ordered
Chemistry	5	Protein
		Lactic acid dehydrogenese (LDH)
		Glucose
		Amylase
Hematology	5	White blood cell count (WBC)
		Wright's stain
		Hematocrit (if pleural fluid is bloody)
Bacteriology	10	Aerobic and anaerobic cultures
		Gram's stain
Tuberculosis and mycology	5	Tuberculosis and fungal cultures
		Acid-fast stain
Cytology	5–25	Cytologic examination
Blood Gas	5	pH
		Pco_2

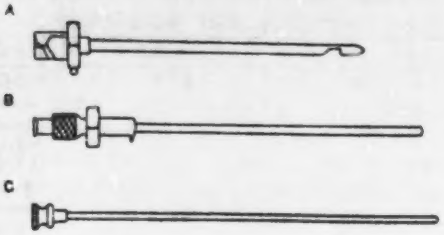
It is unclear why patients feel better after therapeutic thoracentesis since studies have failed to show significant improvement in lung mechanics or gas exchange. Gas exchange may even worsen in some patients. It is likely that relief of dyspnea is related to changes in the geometry of the chest wall or possibly in length-tension properties of the diaphragm and other respiratory muscles (Brown NE et al, Chest 74:540, 1978; Light R. et al, Chest 80:374, 1981; Brandstetter et al, JAMA 242:1060, 1979).

PLEURAL BIOPSY

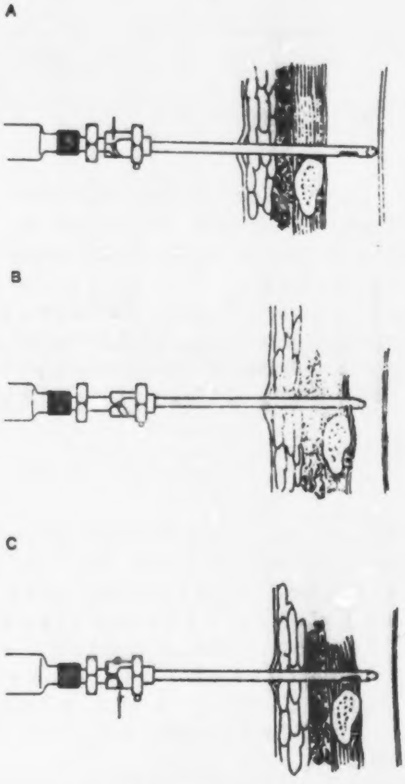
Needle biopsy of the pleura should be performed in almost all patients with exudative effusions of undetermined etiology. At the time of initial thoracentesis, the procedure should probably be performed only when clinical suspicion is high for tuberculous pleural effusion. In a recent study from the Mayo Clinic, cytologic examination of pleural fluid had a significantly higher sensitivity than pleural biopsy in the diagnosis of malignancy (Prakash MS, et al: Mayo Clinic Proceedings 60:158, 1985).

Figure 4 demonstrates the two most common types of pleural biopsy needles and the biopsy technique employed with each.

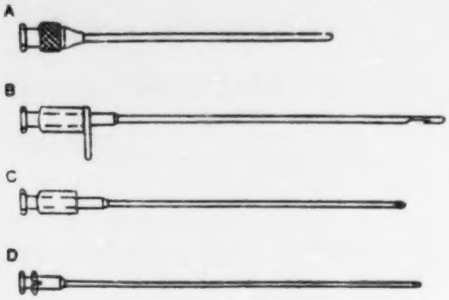
Figure 4



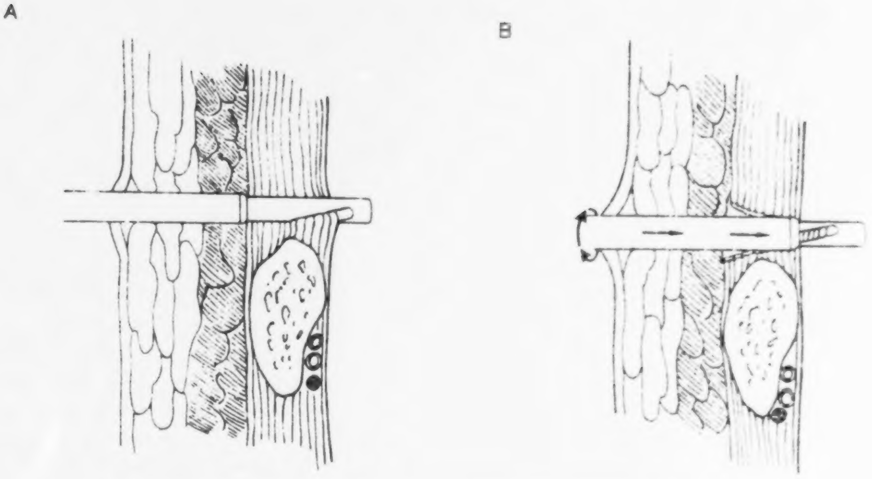
Abram's pleural biopsy needle. *A*, Large outer trocar. *B*, Inner cutting cannula. *C*, Stylet.



A, Abram's needle in pleural space with notch open so that fluid can be aspirated. *B*, Abram's needle snagging the parietal pleura. *C*, The biopsy is obtained when the inner cutting cannula closes the notch in the outer trocar and shears off parietal pleura and anything else that remains in the notch. The arrows point to the pin on the inner cannula that locks into the outer trocar in either the open or closed position.



Cope pleural biopsy needle. *A*, Outer cannula. *B*, Hollow, blunt-tipped, hooked biopsy trocar. *C*, Hollow-beveled trocar. *D*, Obturator or stylet.



A, The parietal pleura is hooked with the hollow, blunt-tipped biopsy trocar. *B*, The biopsy specimen is obtained by advancing the outer cannula with a rotary motion (arrows) to sever the engaged piece of pleura.

Contraindications to pleural biopsy include: bleeding disorders, anticoagulant therapy, and empyema. Biopsies are taken laterally and inferiorly, but not superiorly. (Superior biopsies could injure the neurovascular bundle of the higher rib.)

Diagnostic yield of pleural biopsy can be improved if several samples are obtained on three separate occasions. With this approach, diagnostic yield in tuberculous effusions is over 80%. The yield can be improved to 95% if biopsy material is cultured (8-9). The yield in malignant pleural effusions is 50% overall(8). Complications of pleural biopsy are similar to those of thoracentesis.

Note: All illustrations are taken from Richard Light's book "Pleural Diseases" 1983, Lea and Febiger.

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NEEDLE ASPIRATION

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INTRODUCTION

Percutaneous biopsy of the lungs has been done for years with various cutting needles and even air drills. The first reported culturing of pneumonia from this source came in 1883, while it was first used to diagnose lung cancer in 1886. (2) Currently, the widespread use of the flexible fiberoptic bronchoscope for transbronchial biopsy, and fine needles (18ga-25ga) for aspiration sampling of lungs and mediastinum are safer procedures; larger core and cutting biopsies now are usually limited to pleura or pleural-based masses. Improvements in diagnostic cytopathology and imaging technology (ultrasound, fluoroscopy, computed tomography) are responsible for these advances. Comparative mortality rates reported are: 0 to 0.1% for flexible fiberoptic bronchoscopy (FFB) and needle aspiration; 1.0 to 1.6% for cutting needle biopsy; and 0.9 to 2.6% for open lung biopsy.(1) Transbronchial forceps biopsy through the FFB instrument is generally done for diagnosis, and fortunately yields a relatively large amount of tissue for the pathologist. Transbronchial needle aspiration of mediastinal lymph nodes is usually done for staging after a diagnosis is known, so a cytologic report of definite malignant cells may be adequate without regard to tumor type. While fine needle aspiration (FNA) may be done for staging (especially aspiration of mediastinal nodes, or in patients with multiple lung nodules), it is more often performed for diagnosis. Recognition of specific tumor type on the limited cytology specimen therefore is sometimes essential for key clinical management decisions. The FNA specimen is too minute to be useful in diagnosing chronic diffuse (fibrotic) lung disease or sarcoidosis. (1) By bypassing potential tracheal contamination, FNA can provide more accurate bacterial cultures of pneumonias than transtracheal aspiration or FFB, is less likely to yield multiple pathogens, and still has reasonable patient safety.(3) Transbronchial biopsy or bronchoalveolar lavage (BAL) provides more material to diagnose opportunistic infections and the myriad other causes of infiltrates in immunocompromised patients.

TECHNIQUE

Atropine, 0.6-1.0mg IM, to block vagal reflexes associated with pleural puncture is the only routine premedication; some authors use none. IV access is an appropriate safeguard for all patients, as is nasal oxygen for those with PaO2 under 70-76. A CT scan is necessary only for mediastinal biopsy or in patients with SVC obstruction.(5) A recent chest x-ray assists in positioning the patient on the x-ray table (usually supine or prone), and under fluoroscopy the skin site directly overlying the lesion is marked, prepped, and anesthetized with 1%

lidocaine. Zavala comments that fluoroscopy is unnecessary in some patients with diffuse infiltrates or lobar consolidation.(2) The various needles designed for FNA claim superiority over spinal needles by having non-directional multi-faceted bevels, and thin-wall cross sections often with cutting edges designed to take tiny tissue cores (e.g. E-Z-EN, Greene, Turner).(4) Larger introducer sheaths may be used, some external to the pleura and some passed fully to the lesion to permit multiple aspirates with the biopsying needle hopefully via a single pleural puncture. The rate of pneumothorax relates more to the number of times the pleura is punctured than to the gauge of needle(5), with the exception of the ultrathin 24ga or 25ga aspirating needles, which do reduce this complication without appreciable sacrifice in sensitivity.(1) One to seven passes per procedure are usual. In the case of suspected malignancy, a negative procedure the first time is considered inconclusive. Generally on another day biopsy is repeated, or in a single session a cytologist with microscope may attend in the x-ray suite and, using rapid toluidine blue staining, provide an assessment, even a diagnosis, of each aspirate until adequate material is obtained.(6) During the procedure patients need only hold their breath during the moment of pleural puncture, and otherwise breathe quietly as the needle is advanced in 1 or 2cm increments under fluoroscopy. Following biopsy if fluoro shows no pneumothorax, a chest x-ray is obtained after 2 to 4 hours of observation in the x-ray department (outpatients) or the hospital room (inpatients). Outpatients are then discharged home after being appraised of symptoms to monitor and on the provision they will not be left alone for the next 24 hours. Outpatient biopsy is clearly accepted by most authors (5,6,7) but probably not for patients over 65 or with significant cardiopulmonary disease; even outpatient management of a chest tube for pneumothorax has been advocated. Specimen material for pathology may include: core fragments for imbedding; fixed frosted glass slides (better adhesion of material) for staining, including ones for AFB and fungal stains; tissue fluid and rinse of syringe needle for millipore filtering and stain. Some labs may want the entire specimen in a transport fluid instead, which the cytotechnologist will then centrifuge, making smears from the spun sediment. Ideally, a second specimen is obtained for microbiology; after making air dried frosted glass slides for special stains (including DFA for Legionella, if appropriate), the remainder is transferred either in the aspirating syringe or a sterile tube immediately for lab plating of cultures.(2) Optimal lab support, coordinated in advance of each FNA procedure, is absolutely critical to obtaining meaningful results.

PATIENT SELECTION AND CONTRAINDICATIONS

Fine needle aspiration is indicated when diagnosis of an indeterminate lung or mediastinal lesion is needed, especially when thoracotomy may be spared or is contraindicated. Discrete lung lesions suspicious for malignancy (nodules down to 0.5-1.0cm diameter in some locations) and infiltrates suggesting infection can be aspirated. FFB with biopsy, brushings or other sampling is usually appropriate first, especially to fully examine the airways in cases of suspected new malignancy. (2,5) Almost half of Zavala's 50 patients underwent FNA because of previous non-diagnostic FFB with biopsies, and in 10 of those 22 FNA did yield specific diagnoses; only 1 of the 12 patients undiagnosed by either procedure ultimately proved to have malignancy.(2) Why do FNA if surgery is "inevitable" anyway? Some reasons include better preoperative planning; shorter operation time by eliminating some frozen sections; or unexpected FNA diagnosis of small cell cancer or a definitive benign process, thus eliminating thoracotomy.(5) Of the following contraindications for FNA, only the first four are absolute:

1. Uncooperative/unconsenting patient(4)
2. Suspicion of echinococcal disease(4)
3. Inadequate operator and/or cytopathology expertise(2)
4. Uncorrectable bleeding disorder(2,5)
5. Platelet count under 50,000(7)
6. Prothrombin time prolonged more than 13 seconds(7)
7. Suspected vascular lesion (needs CT exam)(5)
8. Severe bullous disease or FEV 1 less than 1L.(4,8)
9. Contralateral pneumonectomy(8)
10. Pulmonary hypertension(5,8)
11. Mechanical ventilation(3)
12. No planned action, regardless of result(5)

COMPLICATIONS

Older cutting needle biopsies caused deaths from pneumothorax, bleeding and air embolism. Only two deaths are reported by the world literature to have occurred between 1973 and 1981.(5,12) Numerous major series since, some including nearly 2,000 patients, report no deaths from FNA. A few cases of malignant seeding following large-bore lung biopsy in the past have been reported, but experience with thousands of FNA biopsies of various organs at many centers in the last decade has yielded only two reports of seeding.(4,5) No statistical evidence suggests distant dissemination of tumor from bronchoscopic biopsy or FNA; creation of malignant pleural effusion from tumor, or empyema from infection, is not a recognized threat of FNA. Pneumothorax is most common, occurring in 7-35% of patients, requiring chest tubes in 4-14% of patients (and in almost all patients with severe bullous lung disease).(4) Minor hemoptysis occurs in 2-8%, always non-fatal; it is usually brief and occurs immediately post-procedure. Both pneumothorax and hemoptysis occur least in series of patients whose lesions were pleural-based (either on the peripheral chest wall or mediastinum) and biopsied with ultrasound.(9,10)

DIAGNOSTIC INDICATIONS FOR FNA

Diagnosis of lung cancer

Diagnostic yield is especially high by FNA for tumors presenting with SVC syndrome or in the superior lung sulcus (Pancoast tumor).(4,5,11) Diagnostic yield of malignant "coin lesions" in peripheral lung by FNA is 90% by Zavala compared with yields of 30-70% by FFB biopsy.(2) Overall diagnostic rates for lung cancer, primary or metastatic, in the large series referenced here all exceed 80%. Sensitivity improves with a second FNA (e.g. from 87% to 96% in Sagel's group of 896 cancer patients).(4) But many groups determine only malignancy from FNA, without specific cell type in most instances.(4,8,13) In most cases, a pathologic report reading simply "malignant cells present" is adequate to make further diagnostic or therapeutic decisions. Several authors emphasize that lesions with reports of "atypia" or "suspicious for malignancy" from a FNA cannot be accepted as diagnostic. Several groups analyzed their success typing primary lung cancers from FNA aspirates and reported 65-93% accuracy comparing to surgical/autopsy specimens.(7,13,14,15) The toughest problem seems to be differentiating some adenocarcinoma from squamous, and in identifying small cell anaplastic (the classic oat cell subtype is easier, but cytologists may call others just anaplastic or non-specific malignant, or even false-negative for malignancy, perhaps due to necrosis). Clinically, this means some patients with small cell may not be spared by their FNA biopsy from a further surgical procedure to make the diagnosis. But cytopathology experience committed to the medical literature suggests that the worse possibility of false-positive diagnosis of small cell almost never occurs; Thornbury described one without clinical impact (the patient died of undifferentiated large cell) and mentioned three from other reviews.(14) The overall rate of false-positive malignant diagnoses from FNA is less than 1%(4,7,8,14-16) and is usually due to a tuberculous or fungal granuloma which may be mistaken for adenocarcinoma.(4,7) Rarely the FNA may be positive, and histology of the resected piece of lung scar be initially negative but then found to contain tumor after serial sectioning of the entire specimen.(18) For cancer metastatic to the lung, success of FNA in detecting malignancy may be slightly less than for bronchogenic tumor. Those groups analyzing histologic types from their FNA specimens(5,7,14) were most likely to recognize lymphoma, breast, colon, melanoma, germ cell, sarcoma and renal cell tumors as being metastases; especially valuable were comparison slides of patients' original tumors. Special histopathologic techniques for certain tumor cell markers, lymphocyte subtyping, etc. can be valuable even on cytologic specimens.(17) In summary, a clinician with a patient suspected of cancer who has two negative lung biopsies (FFB transbronchial and/or FNA) must be guided by his institution's track record of success at these biopsies, and by his clinical judgment. Outpatient follow-up will be appropriate for some patients in lieu of further diagnostic procedures.

Staging of lung cancer

FNA for staging involves the same decision logic stated above. FNA results, often combined with bronchoscopy and a CT scan, may complete both diagnosis and staging for many patients. FNA of mediastinal abnormalities for staging is intensively reviewed by Weisbrod(5). Its method and technique are the same, but a CT scan is usually indicated first. FNA can sample anterior and posterior mediastinal compartments as well as all major node areas of the middle mediastinum (the carinal area is most difficult, requiring an oblique approach, but FFB transcarinal aspiration would fill that gap nicely). Ultrasound also helps guide biopsy of masses on the peripheral chest or mediastinal pleura.(9,10) One caveat: tumors may abut but not involve mediastinal structures, a fact which CT, FNA or transbronchial aspiration may not distinguish; stage or resectability of these is only determined at surgery.(20)

Diagnosis of benign focal chest lesions.

Unfortunately, two or three nonspecific FNA biopsies without so much as atypia on the reports do not assure benignity, particularly in a group of patients selected for this procedure because of their high risk of having cancer. For some discrete mediastinal masses, especially those cystic on CT scan, FNA can definitively diagnose lipoma, retrosternal thyroid tissue, mesothelioma, foregut or pericardial cyst (fluid containing bronchial epithelial or mesothelial cells, respectively), or aneurysm.(5) For most lung lesions ultimately proven benign surgically, however, only 10-48% can be given a specific benign diagnosis by FNA, while the others are still indeterminate.(4,7,8,13,15) In all series, specific diagnoses are usually tuberculous or fungal granulomas with a rare hamartoma, lipoma or cyst. For lung cavities, Zavala points out that FNA is safe and unlikely to release endobronchial or hematogenous infection, has a good rate of detecting malignancy, and provides culture material free of upper airway contamination.(2) For "coin lesions" obtaining AFB and fungal culture of FNA specimens and waiting the necessary 4-6 weeks for results multiply diagnostic yield several fold over stains alone. Khouri achieved a 48% rate for diagnosing benign lesions by including 26 "nonspecific granulomas" along with 24 granulomas having specific organisms. This is controversial. The other series required organisms and all had less than 25% yield. Calhoun described two FNA biopsies that showed multi-nucleate giant cells but, lacking a proven organism, were called indeterminate and the patients then found to have malignancy.(13) One of these clearly had a granuloma sampled in one of his multiple lung nodules, and the tumor was found in others. Clinicians may still decide on periodic follow-up for many patients with indeterminate lesions, especially after a normal bronchoscopy, and FNA that convincingly sampled the lesions but reported nonspecific inflammation and fibrosis.

Diagnosis of infectious infiltrates

Needle aspiration has been done since the pre-antibiotic days to do serotyping of the pneumococcus. FNA is done primarily now for diagnosis in immunocompromised patients. FNA is occasionally useful for adult or pediatric patients with undiagnosed pneumonia and inability to easily obtain other specimens, reportedly with diagnostic cultures in 50-80%, false negatives in at least 20%, and skin flora contaminants (usually easily distinguished) in 10-20%.(3) By comparison, transtracheal aspiration is associated with fewer false-negative but more false-positive cultures. Bacterial cultures via bronchoscopy and a protected catheter brush require scrupulous procedural technique with quantitative cultures, and also give more false-positive results especially in patients with bronchitis or structural lung disease. Prior antibiotic therapy reduces culture diagnosis of both aerobic and anaerobic infections in all groups of patients. Importance of timely handling of FNA specimens for microbiology is stressed with a good protocol described by Zavala.(2) For the critically-ill immunocompromised patient, especially on a ventilator, the ultrathin 24ga or 25ga neeedle may decrease complications and is certainly adequate to obtain tissue fluids with no need for even tiny cores. Diagnostic rates for bacterial (and fungal) infections in these patients are over 75% (2,4,19) and include various mycobacteria, Legionella, Cryptococcus, Histoplasma and anaerobes.

For AIDS patients most authors recommend bronchoscopic lavage with or without biopsy, since the FNA sample cannot reliably diagnose Pneumocystis, CMV and other viral pneumonias. FNA is inadequate to diagnose most non-infectious diffuse lung insults (pulmonary hemorrhage, radiation or chemotherapy toxicity, so-called cryptogenic pneumonia or diffuse alveolar damage.)

THERAPEUTIC INDICATIONS FOR FNA

Virtually none exist. Large bore or cutting needles may be used to drain/biopsy pleural fluid collections or even abscesses. Speculatively, FNA could be used to drain a large or symptomatic pericardial or bronchogenic cyst in a patient and obviate surgery.

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OXYGEN DELIVERY SYSTEMS

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The purpose of this chapter is to present the different methods available for delivering oxygen, and to briefly discuss the interrelated role of humidification devices. The choice of delivery systems should be determined by 1) the FiO$_2$ desired, 2) the amount of fluctuation in FiO$_2$ allowable, and 3) patient comfort. When prescribing oxygen for ambulatory patients, cost and portability of the system must also be taken into account.

Oxygen delivery devices can be broadly divided into two classes, those which are capable of delivering a relatively constant oxygen concentration in the face of fluctuations in minute ventilation, and those which are not. The two groups are often characterized as high flow and low flow systems respectively. However because of the frequent confusion of high and low flow with high and low concentration (an important distinction), the terms fixed performance and variable performance are used in this chapter to respectively describe the two groups.

VARIABLE PERFORMANCE DEVICES

All of these devices, as noted earlier, are characterized by relatively low gas flow, and as such they depend on the presence of a reservoir of oxygen from which to draw during periods of peak inspiratory flow. The FiO$_2$ delivered varies considerably and in an inverse fashion with changes in tidal volume and respiratory rate. On the whole, these devices are best used when the tidal volume is 300-700ml, the ventilatory rate is below 25/minute, and the ventilatory pattern is regular.

Nasal cannula

The nasal cannula is the best tolerated of any oxygen device and boasts the advantages of lightness, cheapness, and ease of application. It can be kept in place during eating and expectoration and poses no aspiration risk in the event of vomiting. The chief disadvantage, aside from variable FiO$_2$s, lies in its easy dislodgement; in addition, excessive flows can cause nasal and frontal sinus pain due to drying. While mouth breathing doesn't significantly reduce the delivered FiO$_2$ (the narrowing at the oropharynx creates a Bernoulli effect and draws oxygen out of the nasopharynx), the nasal cavities must be patent. The nasal catheter is a similar device, with the distinction of being the oldest unchanged oxygen apparatus still in use, but is less well tolerated by the patient.

Of common oxygen delivery devices, the nasal cannula shows the most variation in FiO_2 with tidal volume changes, since the oxygen reservoir (composed of nasal cavities, nasopharynx, and oropharynx) only comprises about 50cc in the average adult. The actual FiO_2 delivered will depend not only on the oxygen flow rate but even more on the patient's minute ventilation. As an illustration, we will equip a "normal" person, breathing 20 breaths/minute with a tidal volume of 500 cc, an inspiratory time of 1 second, and an expiratory time of 2 seconds, with nasal cannulae at 6 L/min. Since normals will exhale the majority of their tidal volume by 1 second, we can assume exhalation has nearly ceased by 1.5 seconds, allowing the 50cc of anatomic reservoir to just fill in the remaining 0.5 second (6 L/min=100 ml/sec). The next 500 cc inhalation contains 50cc of absolute oxygen from the nasal cavity, 100cc of oxygen from the cannula flow rate, and 350cc of 21% oxygen from room air equating to 73.5cc of oxygen. Thus, the tidal volume breath contains 223.5cc of oxygen, or 44% FiO_2. *If the breathing pattern is constant*, a drop in oxygen flow of 1 L/min leads to a 4% drop in FiO_2.

Nasal cannulae need not equate with low concentration oxygen. If the same scenario is recalculated assuming a 250cc tidal volume, the delivered FiO_2 would be 68%. More often the opposite problem occurs, however, with the tachypneic patient receiving an inspired oxygen concentration barely above room air. With an increase in ventilatory rate less time is allowed for oxygen delivery and any increase in tidal volume further dilutes the oxygen.

Simple mask

All oxygen masks share certain characteristics. They are capable of supplying higher concentrations of oxygen than are nasal prongs, and are unaffected by nasal obstruction. They can also be used with an aerosol nebulizer to deliver high humidity and/or pharmacologic agents. Negative aspects include discomfort because of retained heat and the need for a tight fit, increased risk of aspiration in the presence of vomiting, the need for removal when eating, and greater cost. There is an increase in dead space as well, but this is not a problem unless low flow rates are used (< 5 L/min).

The simple mask is a disposable plastic device without valves or reservoir bag. It is loosely fitted and has expiration ports along either side. When inspiratory flow exceeds oxygen flow (which is nearly always the case), additional air enters through the exhalation holes and around the rim. The mask itself functions as the oxygen reservoir, with achievable oxygen concentrations of 35-45% at 6-10 L/min flows.

Partial rebreathing mask

This is similar to the simple mask, except that a reservoir bag is connected to the mask at the oxygen supply inlet. The reservoir is supposed to supply enough oxygen to meet the flow demand at peak inspiration, and for this reason the bag must never totally collapse. The design of the bag also conserves some oxygen by allowing the first 100-150 cc of exhaled tidal volume to re-enter the reservoir bag. At this point, assuming adequate flow rates, the bag has been distended by a mixture of source oxygen and oxygen-rich air from the anatomic dead space, and the remaining tidal volume containing most of the alveolar ventilation and therefore most of the carbon dioxide is vented out the side ports. If oxygen inflow is sufficient to prevent reservoir collapse during inspiration and is at least 4 L/min, there is negligible carbon dioxide contamination of the reservoir. With flow rates of 6-10 L/min, inspired oxygen concentrations of 40-60% are usually delivered.

Non-rebreathing mask

Similar to the partial rebreathing mask, this device has a one-way valve between the reservoir bag and the mask, and valves over the exhalation ports. The former prevents gas flow from mask to reservoir during exhalation, and the latter prevents room air intake during inspiration. In practice, one of the exhalation valves is removed or another valve is present in the neck or mask to allow intake of room air if delivered flow proves to be inadequate. Because of this, and because of the difficulty in obtaining a true seal around the face, the measured FiO_2 is usually in the range of 60-70% . (Although less practical, concentrations near 100% can be reached using permanent equipment such as a tight-sealing anesthesia rubber mask and a rubber anesthesia bag). As with the partial rebreather, the flow must be adjusted so that the reservoir bag never collapses.

FIXED PERFORMANCE DEVICES

As noted earlier, fixed performance systems are high flow (not necessarily high concentration) devices which offer relatively consistent FiO_2's by supplying all the gases the patient requires during inspiration. The obvious advantage is that minor changes in ventilatory pattern do not affect FiO_2, and since the entire minute ventilation is supplied humidity and temperature can usually be better controlled. The disadvantage is also obvious, in that a large amount of oxygen is wasted during most of the respiratory cycle to keep the flow rate above that of peak inspiration.

Venturi (air-entrainment) masks

Although not actually utilizing a Venturi tube, the principle is similar and the name well-entrenched. Oxygen flows through a restricted orifice, with an increase in velocity and a decrease in lateral pressure because of the Bernoulli effect. Room air is entrained into the stream at the jet site, the final oxygen concentration varying inversely with the size of the lateral fenestrations. Increasing the oxygen flow should increase total gas flow without significantly altering FiO_2. These masks were originally designed for the treatment of CO_2 retaining patients, since they provide reasonably constant low FiO_2's; however, there are inherent pitfalls. Though usually more of a problem with air-entrainment nebulizers than with masks, an increase in back pressure will cause less entrainment and a higher FiO_2. A more common problem is the failure to match or exceed peak inspiratory flow rates - when this occurs, room air "contaminates" the inspired gas mixture. While 40 L/min is usually an adequate flow rate for the quietly breathing patient, the tachypneic patient may have peak inspiratory flows approaching 100 L/min. Matching this flow is no problem at low FiO_2's - with a venti-mask set for 24% oxygen, the air:oxygen ratio is 25:1, so that a priming oxygen flow of 4 L/min supplies gas at 100 L/min, but at an FiO_2 of 40% the air:oxygen ratio is 3:1, so that a priming flow of 15 L/min supplies a gas mixture at a bare 45 L/min.

Since most of the supplied air is room air, humidification of the entrained air is needed if humidification is desired. This is accomplished by the use of humidification cuffs fitting over the entrainment portals, which on most models does not significantly alter the FiO_2.

Air-entrainment nebulizers

The commonest nebulizer in clinical use is the jet nebulizer, utilizing the same principle as the venti-mask to entrain aerosolized water into the stream of gas. Most of these have air-entrainment capabilities as well, delivering anywhere from 30% to 100% oxygen. However, total flows are frequently limited. Maximum oxygen flow to the jet is commonly about 15 L/min, so that any concentration above 50% oxygen provides a total flow that is inadequate even for the quietly breathing patient. Frequently two nebulizers are joined together by a Y-connector to supply a more realistic flow rate. This arrangement is commonly used with a T-piece for intubated or tracheostomy patients, and can also be used with an aerosol mask or a face shield. The latter is a partial mask open at the top. It is a high flow device, and is capable of delivering high concentrations of oxygen, but by its design it is inconsistent and therefore is not truly a fixed performance device.

SPECIAL SYSTEMS

The CPAP (continuous positive airway pressure) mask can be used to improve oxygenation in the same way that CPAP through an endotracheal tube does, i.e. to increase functional residual capacity and thus decrease shunt fraction. The mask can be used in awake cooperative patients who are normo- or hypocapnic when one wishes to avoid intubation and oxygenation cannot be maintained by simpler means. Gas flow is usually supplied from an entrainment nebulizer. Gastric distention and vomiting are potential problems, hence the requirement that the patient be fully awake. Patient acceptance can also be a problem, but a graphic explanation of the alternative may improve compliance.

HUMIDIFICATION

Air inspired through the nose reaches 34°C and 90% relative humidity by the time it reaches the oropharynx, and is 37° and saturated at the carina. If oxygen is administered to a patient with an intact upper airway, all that is needed, unless aerosol therapy is specifically desired, is to humidify the dry source gas to something approaching ambient (e.g. 50%) relative humidity. The simple bubble humidifier, which allows for a high rate of water vaporization by increasing the air-water interface, is the simplest method and is usually more than adequate.

However, when the upper airway is bypassed via intubation or tracheostomy, the supplied gas must be saturated and at or near body temperature. Nebulizers are more frequently used, but either a humidifier or a nebulizer is adequate as long as the device is heated. At room temperature, no matter how consistently the gas mixture is saturated, the result will be inadequate; air which is 100% saturated at 21°C is only 40% saturated at 37°. Indeed the temperature gap is often wider because of the evaporative cooling effect as gas passes through an unheated humidifier or nebulizer. Large bore tubing must be used with heated equipment since precipitation or "rainout" will occur as the gas cools on the way to the patient. Although the nebulizer is often preferred in this situation because it ensures saturation by supplying additional particulate water, more care must be taken to avoid contamination since aerosol particles readily transport bacteria.

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RESPIRATORY THERAPY

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Besides oxygen therapy and mechanical ventilation, which are discussed elsewhere, respiratory therapy offers a number of other modalities for the treatment or prophylaxis of pulmonary diseases. Although it is the respiratory therapist who must thoroughly master the technical aspects of these maneuvers, every practitioner involved in direct patient care should have a working knowledge of their indications and limitations in order to apply them properly.

AEROSOL THERAPY

An aerosol is a suspension of very fine particles of liquid in a gas. An atomizer is a device that generates an aerosol, a nebulizer one that generates an aerosol of uniform particle size. Of the latter, the two commonest types are jet nebulizers and ultrasonic nebulizers. The former utilizes gas flow delivered at high velocity through a narrow orifice, which is directed over the top of a capillary tube. The base of the tube is immersed in the solution to be nebulized. As it emerges from the narrow orifice, the gas flow creates a Venturi effect, with the subatmospheric pressure drawing a constant supply of solution up the capillary tube for dispersal into fine droplets. Some jet nebulizers in common use are 1) mainstream nebulizers, which generate aerosol directly in the main gas flow, and are used to deliver large volumes of aerosol for humidification; 2) sidestream nebulizers, which create aerosol below the mainstream of gas flow, and are used to deliver small amounts of medication over a period of minutes; and 3) metered dose nebulizers, commonly called "inhalers", which deliver a premeasured dose of aerosolized drug with each actuation, using an inert fluorocarbon to power the aerosol. Ultrasonic nebulizers are electrically powered, converting alternating current into an ultrahigh frequency which vibrates a small disc immersed in a couplant fluid. These vibrations are transmitted through a thin membrane directly to the humidifying or medication solution, the intense disturbance breaking up the surface into aerosol which is then carried to the patient by directed airflow. While more expensive, the ultrasonic nebulizer does have the advantage of high volume aerosol output, with more particles of "effective" size (0.5-3 microns).

Aerosols may be bland (water or saline), or may be used to deliver medications. Bland aerosols can be used for humidification of oxygen mixtures, whether delivered by mask or by mechanical ventilation, but they offer no real advantage over heated humidifiers and do carry a higher risk of contamination.

Bland aerosols may also be used to add water to retained secretions to promote their expectoration, something that humidifiers cannot do; however, there is little data to support their efficacy. The term "bland" itself is something of a misnomer, since all aerosols carry the risks of transmission of infection, swelling of retained secretions with resultant airways obstruction, and precipitation of bronchospasm (1).

Aerosols are much more commonly used to deliver medications. Drugs administered by aerosol include beta-agonists, anticholinergics, steroids, and cromolyn sodium. Advantages of the inhaled route over enteral or other parenteral methods of delivery include rapidity of onset and avoidance of side effects. One major drawback of this route of administration is that the dose of medication actually absorbed by the patient is very difficult to control. Aside from the considerations of particle size, stability, electrical charge, and tonicity, which can usually be controlled by the aerosol-generating device, the ventilatory pattern of the patient is crucial in determining deposition (2). The deposition and retention of aerosol particles are related directly to inhaled volume and inversely to ventilatory rate (3). Rapid shallow breathing reduces the concentration of aerosol droplets because of a higher proportion of deadspace in the tidal ventilation, reduces the time available for aerosol droplets to impact on the mucosa, and to some extent reduces penetration into the bronchial tree. This is true regardless of the type of nebulizer used, but is of crucial importance when using a metered-dose inhaler because whatever absorption occurs from each dose must happen in one inhalation. When a metered-dose inhaler is prescribed it is vital that the patient be instructed in proper technique, since left to their own devices up to one half of patients will use it improperly (4). Proper technique consists of actuating the inhaler at the beginning of a slow inspiration to TLC, followed by breath holding for as close to 10 seconds as possible (5). On a follow-up visit the patient should be asked to display his technique to ensure that he is capable of using the inhaler properly.

Even with careful tuition, about 15% of patients seem unable to learn the proper method of inhalation (6). Furthermore, even with optimal technique metered-dose inhalers deliver only about 9% of the aerosol to the lungs, with 80% deposited in the oral cavity and pharynx, and the rest being lost in the actuator or in exhaled air (7). Although dosage adjustment can compensate for this low percentage of delivery, local deposition does increase the risk of oropharyngeal candidiasis. Partly in response to these shortfalls, a number of spacer devices have been marketed for use with metered-dose inhalers. By lengthening the distance from the actuator to the mouth (tube spacer) or by propelling the aerosol into a chamber (reservoir spacer), the aerosol jet is slowed and is therefore less likely to impact in the pharynx.

Also, some evaporation of solvent occurs, decreasing particle size and possibly allowing greater penetration into the airways. By allowing a delay between actuation and inhalation, spacers are also felt to bypass most problems with patient discoordination (8,9).

Studies of drug deposition have supported the contention that spacers improve aerosol distribution. Airways deposition is improved, albeit slightly, and pharyngeal impaction definitely decreased (10,11). When used with inhaled corticosteroids, spacer devices have been shown to decrease the incidence of thrush and dysphonia (12). Studies investigating the effect of spacers in overcoming poor technique are conflicting, but in general it appears that when technique is faulty spacers do improve the effectiveness of a drug delivered by MDI (8). When good technique is used, little or no benefit is apparent, even though studies of particle deposition suggest some theoretical advantage (13).

When compared to "nebulizer" therapy (i.e. medication delivered by a sidestream nebulizer powered by a compressor), metered-dose inhalers with spacers have been shown to be as effective in the treatment of airways obstruction (14-16). However, patients with severe airways obstruction have not been systematically studied, and few series have looked at spacers in decompensated asthma or COPD. One study noted that as the degree of obstruction increases, delivery by nebulizer appears to show an advantage over the metered-dose inhaler (17). Intermittent positive-pressure breathing (IPPB) is still used to deliver aerosol in some hospitals, but it is more expensive and more hazardous than the simple sidestream nebulizer, and has been shown to be no better (18). At present, delivery of drug by passive inhalation from a sidestream nebulizer is still the method of choice in acute exacerbations of obstructive pulmonary disease.

In summary, although the role of bland aerosols is controversial, aerosolization is an effective means for delivering drugs. For outpatient therapy, the metered-dose inhaler is usually sufficient as long as adequate demonstration is provided. If the patient seems unable to coordinate actuation with inhalation, or if inhaled steroids are prescribed, the patient may benefit from the use of a spacer device as well. When obstruction is so severe that the delivery of aerosol by single inhalations is hampered, administration of medication via a compressor-driven nebulizer may be indicated.

CHEST PHYSIOTHERAPY

In a now famous editorial, Murray likened chest percussion and postural drainage (CPPD) to "getting ketchup out of a bottle:

turn it upside down, thump it on the back several times, and a splash of the desired material usually appears" (19). Although the method has been in use in one form or another for most of this century, there is a good deal of contention about its utility, in part because of its frequent misapplication. Admittedly, even when used in appropriate patients there is little evidence that it affects the natural history of the underlying disease.

CPPD is based on two tenets, that in many patients with airways disease the mucociliary clearance elevator is impaired, leading in some to retention of excessive secretions, and that the retention of those secretions is potentially harmful. The former point is incontestable; the latter has been accepted more on intuition and clinical experience than on evidence. Certainly mucus transport is severely impaired in chronic airways obstruction and is largely supplanted by cough. Yet while mucociliary clearance normally extends to the 16th airway generation, cough appears to be ineffective beyond the 6th generation (20). The linear flow velocity necessary to shear off bronchial secretions can only be achieved in larger airways, and in the presence of marked peripheral airways resistance this may even be limited to the first two airway generations (21). The effect of chest percussion appears to be mobilization of peripheral secretions into more central airways where they can be more effectively cleared by cough. How this occurs has been the subject of much speculation, which was recently reviewed by Wanner (22). King and coworkers have shown that, in the complete absence of cough, high frequency chest wall oscillation in dogs increases tracheal mucociliary clearance to 340% of control, the effect being maximal at 13 Hz (23). In a later study they demonstrated that the same oscillatory pattern applied at the airway opening had no effect on clearance. Peak expiratory flow was found to be twice as high as peak inspiratory flow during chest wall oscillation, while airway oscillation produced equal values, implicating two-phase flow of mucus in a central direction as a potential mode of action (24).

Results of clinical studies concerning the efficacy of CPPD have been conflicting, sometimes for identifiable reasons. In the settings of pneumonia (25) and acute exacerbation of COPD without excessive sputum (26), chest physiotherapy has been shown to be of no benefit. (This is hardly surprising, since there is no reason why parenchymal inflammation or bronchospasm should improve with CPPD, although such applications have been common in the past). When physiotherapy was applied to one group of patients with a hodgepodge of acute and chronic respiratory disorders, those with scant sputum production during physiotherapy experienced desaturation following the session, whereas those with significant sputum production showed no change in saturation (27). In the latter group any tendency to desaturate may have been offset by the improvement in regional ventilation that resulted from clearance of secretions. On the other hand Mohsenifar et. al., studying patients with stable COPD, found no difference in blood gases or spirometry following CPPD - none of these patients produced more than 30cc of sputum per day at baseline (28). Similar results were demonstrated in another study of 35 patients with stable chronic bronchitis, with no significant differences in spirometry or blood gases following either chest percussion or sham treatments; however, no data on baseline sputum production were given (29).

Studies in groups of patients with more appreciable sputum have demonstrated significant differences following treatment, though whether these were clinically significant or not is less clear. Feldman and coworkers found that CPPD increased flows at high and low lung volumes in nine patients with cystic fibrosis (CF) while a similar group of chronic bronchitics showed improvement in air flow only at low lung volumes (30). deBoeck compared cough to chest physiotherapy in a group of patients with CF and found that physiotherapy significantly improved flow at low (though not at high) lung volumes, whereas cough showed insignificant improvement at either volume (31). This is consistent with the postulated site of action for physiotherapy, since flow at low lung volumes is thought to reflect the extent of obstruction of more peripheral airways.

Chest physiotherapy has been extensively studied using radiolabelled aerosol clearance techniques. Wong found that the abnormal tracheal mucus clearance rates in patients with CF reached normal values when they were tilted in a head-down position (32). However, Oldenburg and coworkers found that, when cough was prohibited, postural drainage had no effect on clearance, (33) and in another study postural drainage alone was the least effective modality in improving central mucociliary clearance (34). The last study compared various interventions to spontaneous cough alone and found that, while all showed some improvement in clearance, directed vigorous cough was just as effective as chest physiotherapy. However, the technique that was employed primarily labeled the large central airways, where cough is most effective. Bateman et al studying ten patients with stable COPD and highly productive coughs demonstrated increased clearance after chest physiotherapy when compared to spontaneous cough alone (20). Since the effects of cough training were not controlled in this study, the same group later examined chest physiotherapy with cough versus directed cough alone, studying central and peripheral aerosol clearance in patients with large daily sputum production. Central clearance was similar between the two methods, whereas peripheral clearance was enhanced only by CPPD (35).

Chest physiotherapy can be effective in promoting clearance of secretions in patients with airways disease, as long as it is properly applied. Patients should obviously produce enough sputum to warrant the therapy, since "the bottle must contain some ketchup before it can be emptied" (19). Patients producing more than thirty mls of sputum per day may benefit, especially those with a weak cough, or those with truly copious secretions.

PREVENTION OF POSTOPERATIVE ATELECTASIS

Because of the frequency and potential severity of pulmonary complications following thoracic and upper abdominal surgery, numerous methods for preventing post operative atelectasis have been attempted in the past, the number of techniques testifying to their incomplete success.

IPPB was one of the earlier methods used but was associated with numerous drawbacks. Since it is delivered by a pressure-cycled ventilator, the patient with significant postoperative pain could forcibly prevent chest expansion or simply close his glottis, exceeding the pressure limit without adequately inflating his lungs. On the other hand, the patient with highly compliant lungs could be at risk of barotrauma, a particular hazard in bullous emphysema. As it is routinely applied, IPPB does not alter the incidence of postoperative respiratory problems, and more frequent administration is prohibitively expensive (36). When considering a prophylactic measure applied to large numbers of patients, cost becomes a crucial factor.

Expiratory maneuvers such as blow bottles were widely used in the 1960's. Results were often disappointing, and the technique was never well studied. Blowing water from one bottle to another required more pressure than volume, so that significant chest expansion was not achieved (36). Rebreathing techniques to induce hyperventilation enjoyed some popularity (37), but were largely ineffective because patients tended to increase rate rather than tidal volume.

The incentive spirometer is the most popular method at the present time for prophylaxis of atelectasis (38). It is performed by having the patient take a deep breath through the device, which records volume or flow and indicates when a preset goal has been reached. This should be performed every hour while awake, for 5 minutes at a time. Incentive spirometry is effective for postoperative prophylaxis (39), and since it requires infrequent attendance by personnel after the initial demonstration, costs are minimized.

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MECHANICAL VENTILATION

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INTRODUCTION

The goal of mechanical ventilation is to provide adequate oxygenation and alveolar ventilation. In addition, the requisite intubation allows for protection of the airway. With some exceptions, the most common indications for mechanical ventilatory support are listed in Table 1.

Table 1. Indications for mechanical ventilatory support.

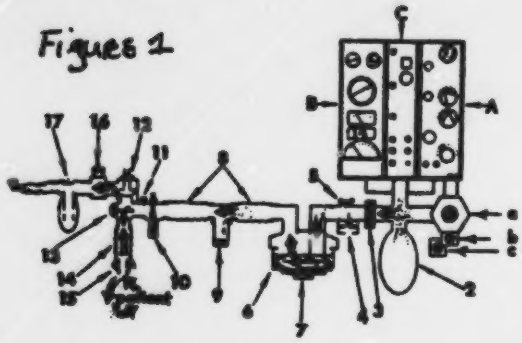
Indications	Clinical Criteria	Potential Causes
Ventilatory failure		
- from decreased respiratory drive	- $\uparrow PaCO_2$ ($>$ 55 torr) - bradypnea - apnea	- Neurological dysfunction, drugs
- from ventilatory muscle fatigue resulting from working on stiff or obstructed lungs	- $\uparrow PaCO_2$ ($>$ 55 torr) - tachypnea ($>$ 35BPM) - muscle weakness ($<$ 25cm H_2O negative inspiratory force) - $\downarrow C_L$ - $\uparrow R_{AW}$	- Obstructed lung disease - Restricted lung disease - Endotracheal intubation for airway protection
- from ventilatory muscle fatigue resulting from large deadspace ventilation requirements.	- $\uparrow PaCO_2$ ($>$ 55 torr) - tachypnea ($>$ 35BPM) - $\uparrow V_D/V_T$ ($>$.6)	- Pulmonary vascular disease
Oxygenation failure	- $\downarrow PaO_2$ ($<$60 torr on maximum face mask supplementation	- Any pulmonary process resulting in abnormal $\dot{V}/\dot{Q}$ relationships or shunts

CLASSIFICATION AND FUNCTION OF MECHANICAL VENTILATORS

Components

Mechanical ventilator components may be grouped into the following categories: controls, monitors, alarms, external features and accessories. The availability, flexibility and level of development of each of these items varies considerably from one ventilator to another. Figure 1 illustrates some of these components.

Figures 1



Major components and accessories of ventilators. (A) Controls; (B) monitors; (C) alarms; (1) gas mixer (a, O_2; b, CO_2; c, N_2O); (2) IMV-CPAP system; (3) bacterial filter; (4) safety "pop-off" valve; (5) safety inlet valve; (6) humidifier-nebulizer; (7) heater for humidifier or nebulizer; (8) large-bore delivery tubing; (9) water trap; (10) small drug nebulizer; (11) gas sampling port for monitoring FiO_2; (12) exhalation valve; (13) thermometer; (14) flexible tubing; (15) slip-proof connector; (16) PEEP device; (17) exhaled air scavenger.

Table 2 classifies and lists capabilities and special features of most available ventilators. Pressure support ventilation (PSV) and high frequency positive pressure ventilation (HFPPV) should be included under special techniques since they are now available with some ventilator models.

TABLE 2

Ventilator Classification

	Inspiratory Phase					*Change From Inspiratory to Expiratory*			*Expiratory Phase*			*Change From Expiratory to Inspiratory*			
	Flow Generator		*Pressure Generator*												
Ventilator	*Constant*	*Nonconstant*	*Constant*	*Nonconstant*	*Inspiratory plateau*	*Time-cycled*	*Pressure-cycled*	*Volume-cycled*	*Retard pressure*	*Subambient pressure*	*Threshold pressure (PEEP)*	*Assistor*	*Controller*	*Assistor-controller*	*IMV*
BABYbird	X					X				X	X		2		X
Bourns															
LS 104-150	X						2	X			X	X	X	X	X
Emerson 3PV		X				X					X	•	X		
Emerson IMV		X				X					X		2		X
Siemens 900(B)	X	X			X	X	2		X		X	X	X	X	X
Ohio 560	X				X		2	X		•	X		X	X	
Ohio 550		X						X			•		X	X	
Bennett MA-1	X						2	X	X	•	•	X	X	X	
IMVbird		X				X			•	X	X		2		X
Bird Mark 6			X		X		X				X	2	X		2
Gill 1			X		X		2	X			X	X	X	X	X
Searle	X				X		2	X			X	X	X	X	X
Monaghan 225	X					X	X	X			X	X	X	X	
Veriflo															
CV 2000	X					X					X	X	X	X	X
Veriflo															
CV 200	X					X					X	X	X	X	X
Engström															
ER 300		X			X	X			X		X		X		
Engström															
ECS 2000		X			X	X				•	X		X	X	
Foregger 210	X				X	X	2				X		X	X	X
Bourns Bear 1	X	X			X		2	X			X		X	X	X

X = Primary function
2 = Alternate method of adjustment
• = Optional

Classification

Although traditionally ventilators have been classified into either volume or pressure types, a better classification is that suggested by Kirby in which they are classified according to the phases of the mechanical ventilatory cycle. (Table 3)

Table 3

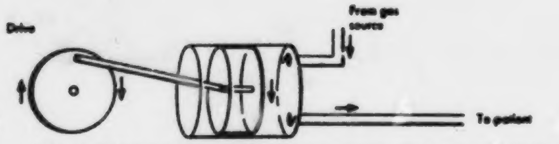
VENTILATOR CLASSIFICATION

- Inspiratory phase
- Flow generator
  - Constant
  - Non-constant
- Pressure generator
  - Constant
  - Non-constant
- Inflation hold
- Change from inspiration to expiration
  - Pressure-cycled
  - Time-cycled
  - Flow-cycled
- Expiratory phase
  - Retard
  - ZEEP
  - PEEP
  - NEEP
- Change from expiration to inspiration
  - Assist (patient-triggered)
  - Control (including IMV)
  - Assist-control

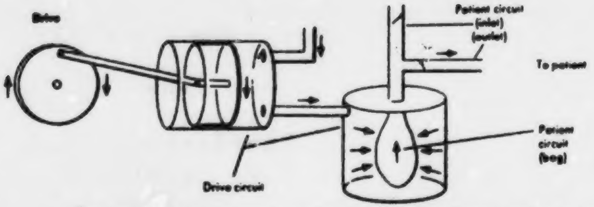
Inspiratory Phase

Ventilators must have a system that produces the force required to generate gas flow. Basic knowledge of these systems is important because it may reflect on the performance characteristics of a particular ventilator. Flow systems can be classified as being composed of single or double circuits. A single system is one in which the gases within the driving mechanism go directly to the patient. In a double system, the gases from the driving mechanism are used to compress another system, usually a bag or bellows, which contains the mixture of gases delivered to the patient (Figure 2).

Figure 2



Single-circuit drive mechanism. In this example, gas passes directly from the cylinder to the patient circuit. The drive mechanism is a rotary-driven piston. (Reprinted with permission from Spearman CB, Sheldon RL (eds): Egan's Fundamentals of Respiratory Therapy. 4th Ed. Mosby, St. Louis, 1982).



Double-circuit drive mechanism using a rotary-driven pision. Gbs passes from the cylinder to a rigid cannister and compresses a bag. Gas contained within the bag is then delivered into the patient circuit. The two gas sources are separate. A collapsible bellows may be substituted for the bag in the patient circuit. (Reprinted with permission from Spearman CB, Sheldnn RL (eds): Egan's Fundamentals of Respiratory Therapy. 4th Ed. Mosby, St. Louis, 1982).

The mechanisms producing the force and air flow are either piston or pneumatically driven.

1. Piston Driven Ventilators

Piston driven ventilators can be subdivided into those in which a rotatory device is used (e.g. Emersons) and which deliver flow in a non constant fashion during the inspiratory phase, or linearly driven ones, in which the piston moves at a constant rate of speed producing a constant flow rate during inspiration.

2. Pneumatically Driven Ventilators

Pneumatically driven ventilators utilize compressed gases as their driving force. These are subdivided into high pressure or low pressure driven systems. With high pressure systems, a high pressure source gas delivers pressures 2 to 35 times that at the airway. In order to protect the patient from these high pressures a valve of variable resistance is used which regulates pressure and flow rate. The flow generated by these systems is constant, and therefore a "square wave" pattern is produced.

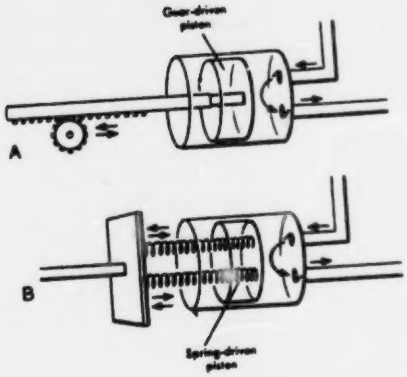
Some ventilators utilize a Venturi device or an injector as their driving mechanism and are classified as low pressure drive systems. A high pressure gas drives the jet of the Venturi. The pressure generated is less than but proportional to the pressure applied to the jet.

With these two types of systems, changes in airway resistance or pulmonary compliance can produce decreases in flow of the pressure in the airways ever equals or exceeds the maximal generated pressure.

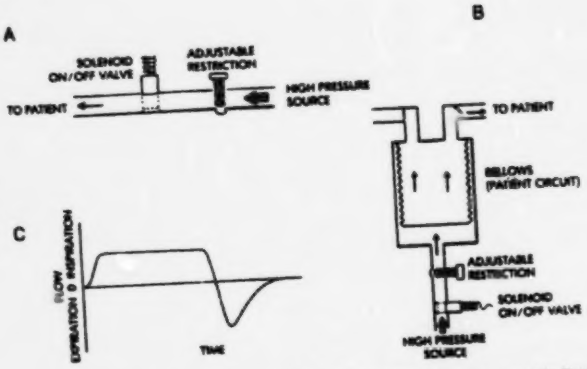
Other ventilators combine the use of compressors and the Venturi principle and are capable of producing pressures in the 120cm H_2O range with flow rates greater than 100 L/min. Some also have the capabilities to deliver different flow patterns (e.g. Servo 900c). Figures 2 and 3 illustrate some of these concepts.

Therefore, ventilators can be divided into constant (CFG) or non constant (NCFG) flow generators depending on which mechanism (discussed above) is used to produce air flow. Constant flow generators are those in which flow is generated by linearly driven piston or pneumatic devices (Puritan-Bennett MA-I) and non constant flow generators those in which flow is generated by a rotary driven piston or modification of it (Emersons).

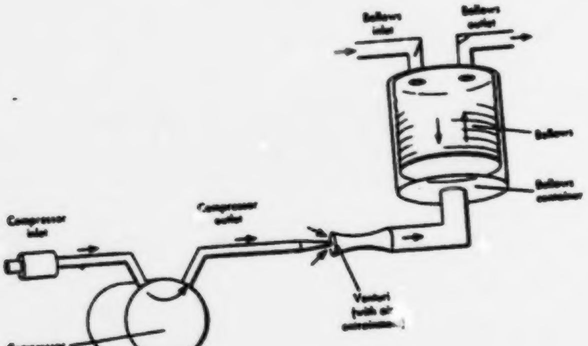
Figure 3


Gear-driven piston
A
B
Spring-driven piston

Single-circuit gear (A) and spring (B) piston drive mechanisms. (Reprinted with permission from Spearman CB, Sheldon RL (eds): Egan's Fundamentals of Respiratory Therapy. 4th Ed. Mosby, St. Louis, 1982.)


A
SOLENOID ON/OFF VALVE
ADJUSTABLE RESTRICTION
HIGH PRESSURE SOURCE
TO PATIENT
B
TO PATIENT
BELLOWS (PATIENT CIRCUIT)
ADJUSTABLE RESTRICTION
SOLENOID ON/OFF VALVE
HIGH PRESSURE SOURCE
C
FLOW
EXPIRATION 0 INSPIRATION
TIME

High-pressure pneumatic drive systems with high internal flow resistance. (A) Single-circuit system. (B) Double-circuit system. Adjustable restrictions control flow from high-pressure source gas. Electrical solenoids open (solid line drawings) and close (dashed line drawings), creating inspiration and expiration, respectively. (C) Constant inspiratory flow pattern typical of these systems.


Bellows inlet
Bellows outlet
Bellows
Bellows container
Compressor inlet
Compressor outlet
Venturi (with air entrainment)
Compressor

Double-circuit compressor-bellows drive mechanism using a venturi. The pressure decrement occurring through the venturi tube increases output from the compressor while additional ambient air is entrained. (Reprinted with permission from Spearman CB, Sheldon RL (eds): Egan's Fundamentals of Respiratory Therapy. 4th Ed. Mosby, St. Louis, 1982.)

Constant flow generators produce gas flow at a uniform rate (square wave) and non constant flow generators produce flow rates that vary through inspiration (sine wave) although variability is constant from breath to breath (Figure 4).

Ventilators that deliver a "sine wave" (NCFG) pattern may improve gas distribution and alveolar ventilation in selected patients with noncompliant lungs or with any other disease process in which simultaneous inflation of lung units with different time constants is required.

Figure 4

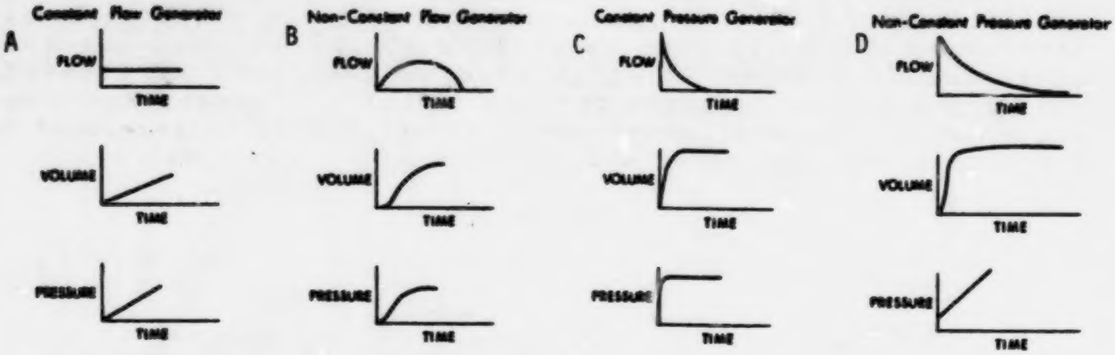


Figure 5

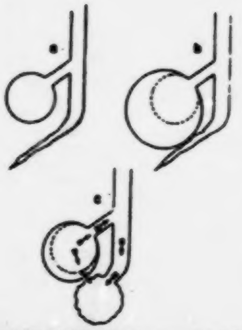


Fig. 3. The proposed effect of inflation hold on lung segments with different filling time constants (i.e., rapid and slow filling areas). (A) normal expanded and abnormal collapsed segments; (B) initial ventilator inflation hyperexpands (over-inflates) normal area, while abnormal area receives little or no flow or volume; (C) prolongation of the inspiratory time (inflation hold) may allow some of the excess gas delivered to the normal area to redistribute itself internally to the area of collapse. The efficiency of ventilation thereby is increased.

Pressure generators may also be constant (CPG) or non constant (NCPG) as shown in Figure 4 C,D. CPG's sustain a uniform pressure throughout the inspiratory phase regardless of changes in pulmonary mechanics. NCPG's develop variable pressure throughout inspiration; however the pressure pattern is the same from breath to breath. Pressure generators are generally used for IPPB therapy.

Inflation Hold (Inspiratory Pause)

This "no-flow" state of the inspiratory cycle is produced by delaying the opening of the exhalation valve. Theoretically, inflation hold allows a longer time for delivered gas to be distributed throughout the lung, potentially improving alveolar ventilation and gas exchange; however, the clinical significance of this remains controversial. (Figure 5) Actually, the greatest value of inflation hold has been in the determination of static lung compliance (See section on respiratory monitoring).

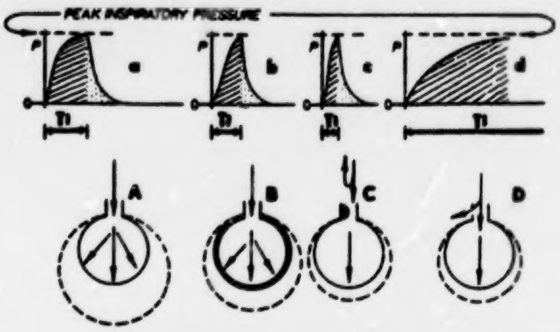
Change Over From Inspiratory to Expiratory Phase

This is accomplished by one of three mechanisms.

1. Pressure Cycling

Pressure cycled ventilators terminate the inspiratory phase when a preselected pressure is achieved within the circuit. Tidal Volume (V^T) and inspiratory time (TI) are directly related to pulmonary compliance and inversely to airway resistance. Therefore, preselected pressures can be reached earlier when airway resistance increases or lung compliance decreases, potentially compromising the actual tidal volume delivered (Figure 6). These are described as increasing pressure-decreasing flow devices. In addition they are usually powered by oxygen at 50 psi with a Venturi as the flow generator, so that as the pressure gradient decreases so does the amount of air entrained, thereby increasing the FiO_2. These devices have limited clinical utility and are used primarily for IPPB therapy.

Figure 6



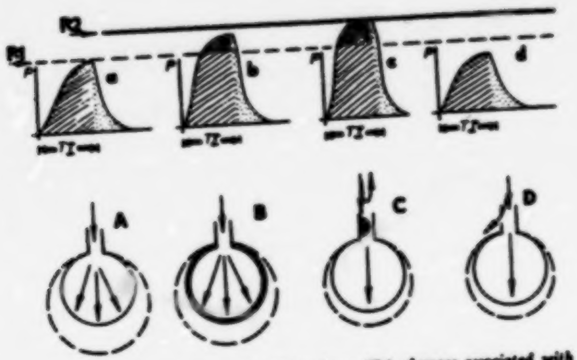
Airway pressure (P), inspiratory time (TI), and tidal volume (V_T) changes associated with pressure-cycled ventilators. In each of the four examples (a, b, c, and d), peak flow (not illustrated) and inspiratory pressure (or cycling pressure) are constant, but TI is altered owing to changes in airway resistance and pulmonary compliance. (A) Healthy lung (desired V_T); (B) lung with decreased compliance (decreased V_T); (C) lung with partially obstructed airway (decreased V_T); (D) leak in ventilator circuit (decreased V_T).

2. Volume cycling

Volume cycled ventilators terminate the inspiratory phase following delivery of a preselected volume of gas. The tidal volume is developed by compression of a bellows (Puritan-Bennett MA-1) or by a flow generator interfaced with a flow sensor (Bourns Bear-1) (Figure 7). The actual volume delivered to the patient is influenced by the volume lost by compression within the ventilator circuit. This compression volume is dependent on the volume and compliance of the entire ventilator-patient circuit and on the peak inspiratory pressure. It is estimated to be 3-5ml/cm H_2O for most adult ventilators.

Therefore, when lung compliance is severely decreased a significant portion of the tidal volume may be lost in the ventilator circuit. Conversely when compliance increases, a greater portion of the selected tidal volume may be delivered, predisposing the patient to barotrauma and/or cardiovascular instability (See Figure 7).

Figure 7



Pressure (P) and tidal volume (V_T) changes associated with volume-cycled ventilators. In each example (a, b, c, and d), inspiratory time (TI) and preset volume (not illustrated) are constant. Peak airway pressure with reference to the desired peak airway pressure (P-1) and safety "pop-off" airway pressure (P-2) and delivered V_T may change owing to alterations in airway resistance and pulmonary compliance (A) Healthy lung (desired V_T); (B) lung with decreased compliance (desired V_T); (C) lung with partially obstructed airway (decreased V_T); (D) leak in ventilator circuit (decreased V_T).

3. Time Cycling

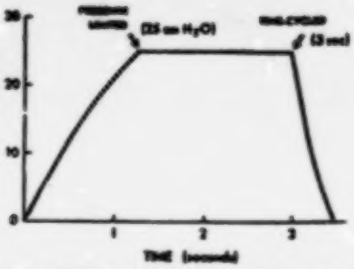
These ventilators terminate the inspiratory phase after a preselected time interval has elapsed. Since most of these ventilators are flow generators they maintain a relatively constant tidal volume. Cycling phases are determined by manipulating one or more of: inspiratory and expiratory time, inspiratory and total ventilatory cycle time, or inspiratory and end inspiratory plateau time as a percentage of total cycle time. The tidal volume is dependent upon the inspiratory time and flow rate. The ability to allow for changes in I:E ratio while keeping delivered tidal volume relatively constant give these ventilators great clinical utility and versatility.

4. Flow Cycling

With flow cycled ventilators gas delivery is terminated when a minimum flow state occurs. None of these ventilators is used in clinical practice today.

Some ventilators provide more than one cycling mechanism usually as a safety feature (Puritan- Bennett MA-1, MA-2, have second pressure cycling mechanism). Others are time cycled but pressure limited (e.g. Baby Bird). In this situation, flow ceases when a selected pressure is reached, however inspiration continues giving an inflation hold effect (Figure 8).

Figure 8



Difference between "Limit and Cycle." A preselected pressure limit (25 cm H_2O) is achieved a little more than one second into the inspiratory phase. Additional flow continues but is dissipated to ambient (does not further increase V_T). The ventilator cycles from inspiration to expiration at 3 seconds. In effect, the time from the pressure limit to cycling represents an inflation hold.

Expiratory Phase

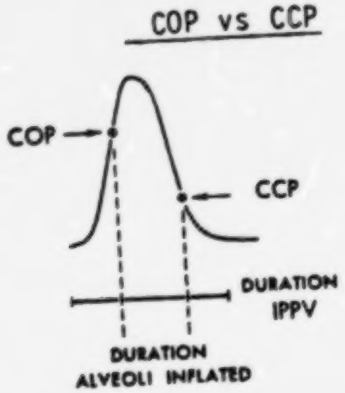
Mechanical exhalation commences when the exhalation valve opens. Pressure may return rapidly to baseline or the valve may be depressurized gradually to provide resistance (retardation). The valve may also remain pressurized to apply positive end-expiratory pressure.

1. Expiratory Retard is sometimes applied to simulate "pursed lip" breathing in an attempt to prevent premature airway closure and air trapping. The indications are debatable but generally include situations in which the inspired mechanical tidal volume is greater than the expired one. Apart from acute and chronic obstructive pulmonary disease the most common cause of air trapping is iatrogenic, secondary to excessive ventilator cycling or delivery of large tidal volumes. Expiratory flow retardation is produced by the attachment of a cap with various orifice sizes to the exhalation valve. In the case of the Puritan-Bennett MA-1 and MA-2 ventilators, an exhalation valve which inflates during inspiration and deflates slowly during exhalation (mushroom type) creates a similar exhalation flow retard effect.

2. PEEP is produced by maintaining a residual pressure at the exhalation valve during the mechanical expiratory phase. When the patient's expiratory pressure equals the PEEP, exhalation ceases and the lungs remain inflated at an increased volume.

Although some alveolar collapse is normal in certain (especially older) patients, in some disease states such as non-cardiogenic pulmonary edema alveolar collapse is so extensive that oxygenation is critically impaired. Before alveolar inflation can occur, a critical opening pressure (COP) must be reached (Figure 9). During exhalation volume and pressure decrease to a level that is insufficient to maintain alveolar inflation and collapse recurs. This point is the critical closing pressure (CCP). When PEEP is applied at a level greater than the CCP of an inflated alveolus, its collapse will be prevented. Because CCP is not uniform for all alveoli, a uniform level of PEEP may not suffice for maximum alveolar recruitment.

Figure 9



PEEP can be applied to both spontaneously and mechanically ventilated patients by several different devices.

A. Underwater column - by this simple method exhaled gas is vented to the atmosphere after bubbling through a water column which is adjusted to the level of water pressure desired. When mean airway pressure equals water pressure, expiratory flow ceases and lung volume cannot be reduced further. The intent is to leave some trapped gas behind to increase FRC. Since neither the entry nor the exit port on the water column is restrictive, there is little terminal flow resistance or flow retard effect (Figure 10A).

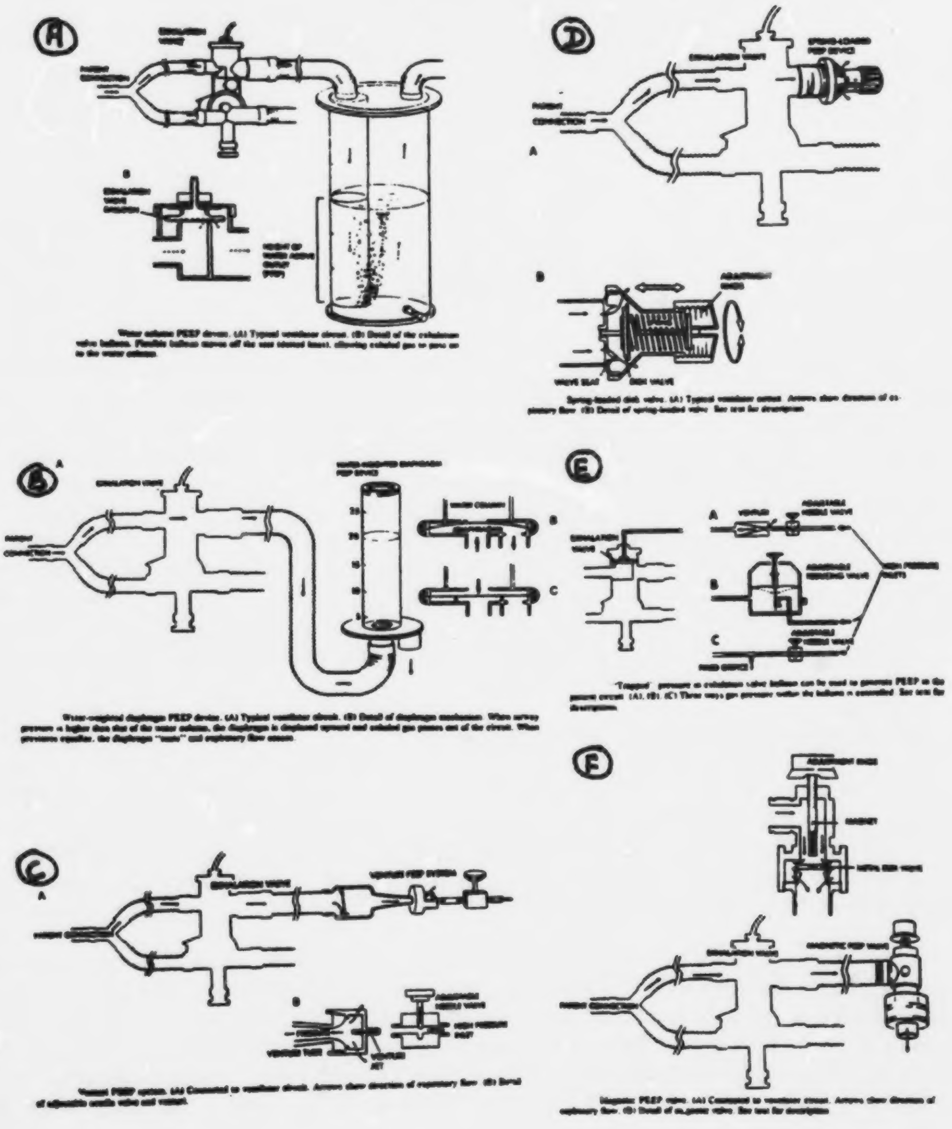
b. Water-Weighted Diaphragm This device is used in Emerson ventilators. Exhaled gas does not bubble through water but instead gas and water are separated by a moveable diaphragm. Airway pressure below the diaphragm needs to exceed that exerted by the water column in order for gas to pass to the exhalation port. This system also offers little resistance to flow or retard effect (Figure 10B).

c. Venturi PEEP Valve- In this system a high pressure gas delivers the jet of the Venturi against a one way valve, through which exhaled gas must pass. When pressure in the airway exceeds that applied by the jet, air moves out through the valve and tubing to the atmosphere. Depending on the resistance to flow offered by the valve, a flow retard effect may or may not occur (Figure 10c).

D. Spring Loaded Disc Valve - Here, an adjustable spring applies tension to a disc located on the exhalation port. The principles of how PEEP is produced are similar to other devices discussed. Whether significant resistance to flow will occur will depend on the length of the spring and the area of the opening for gas flow (Figure 10d).

Figures 10e, f, illustrate two other PEEP devices, the pressurized exhalation balloon (Bourns Bear 2, Puritan-Bennett MA-2 ventilators) and the magnetic PEEP valve concept.

Figure 10



The most common indication for the use of PEEP is in the management of patients who remain hypoxic in spite of therapy with high tidal volumes and FiO_2's >0.50. PEEP is added only after volume overload, cardiac failure, pneumonia, and atelectasis secondary to secretions have been ruled out as causes of hypoxemia.

PEEP improves oxygenation by increasing the functional residual capacity (FRC) of the lung, and decreasing shunt fraction. This is done by recruitment and distention of previously collapsed alveoli. In addition, PEEP may redistribute the fluid within alveoli so that a thinner layer lines them, creating less of a barrier for diffusion. PEEP can also improve lung compliance so that increases in lung volume occur with less change in transpulmonary pressure. Some available data also suggest that PEEP therapy may help to conserve alveolar surfactant.

There is, however, no clinical evidence that PEEP improves underlying lung pathology or prevents the development of ARDS or pulmonary edema when used early in high risk patients.

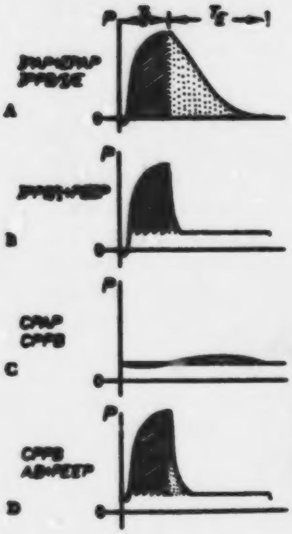
In spite of its beneficial effects, PEEP therapy is frequently associated with a variety of complications which limit its clinical utility and complicate the course of many patients so treated. Table 4 lists contraindications to the use of PEEP, some of which are relative. Adverse effects and complications of PEEP therapy will be discussed in the section "Complications of Mechanical Ventilation". Figure 11 shows a graphic representation of PEEP and CPAP superimposed on various ventilatory modes.

Table 4

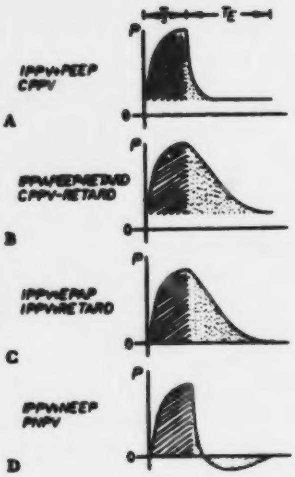
RELATIVE CONTRAINDICATIONS TO PEEP

Emphysema
Bronchitis
Asthma
Unilateral lung disease
 (e.g., pneumonia, pulmonary edema)
Pneumothorax
Bronchopleural fistula
Hypovolemia
Sympathetic dysfunction
Intracranial hypertension
Intracardiac shunt

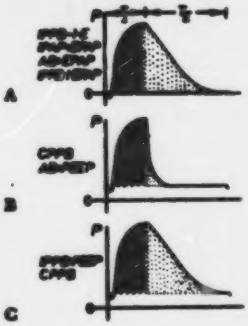
Figure 11



Various forms of inspiratory and expiratory airway pressure applied during spontaneous breathing. (A, B) Intermittent application of positive inspiratory and expiratory pressure. During initiation of inhalation the airway pressure drops below atmospheric pressure (indicated by shaded area below 0). (C, D) Continuous application of positive pressure.



Inspiratory positive and expiratory positive or negative airway pressure during controlled ventilation. (A) Pressure curve represents CPPV when PEEP is generated by threshold resistance. (B) Pressure curve represents CPPV when PEEP is generated by flow resistance. (C) Pressure curve represents IPPV with retarded exhalation. In such situations expiratory pressure may reach atmospheric levels. (D) Pressure curve represents IPPV + NEEP. Negative pressure is applied at some point during the expiratory phase. (This technique is seldom used in modern ventilatory support.)



Pressure curves representing application of mechanically induced positive inspiratory and expiratory airway pressure during assisted breathing. (A) IPAP + EPAP when expiratory positive pressure is generated by retarded exhalation (though it ultimately returns to atmospheric level if a sufficient duration of exhalation is provided). (B) Continuous positive pressure when PEEP is generated by threshold resistance (PEEP-compensated). (C) Continuous positive pressure when PEEP is generated by flow resistance (PEEP-compensated).

Changeover From Expiratory to Inspiratory Phase

1. Control Mode - This type of ventilation is provided when a positive pressure breath is delivered at a preselected time interval regardless of patient's effort. The control rate is provided by electrical timers which can be of several types: single rate (BPM), inspiratory and expiratory timers (independent control of inspiration and expiration), or independent expiratory timers (inspiration begins when a selected expiration time ends).

In this ventilatory mode, precise delivery of flow patterns or alterations in I:E ratios (e.g. reverse I:E ratio) can be achieved in order to improve distribution of ventilation and promote alveolar stability.

Although ventilatory drive can be suppressed with high levels of control ventilation, patients frequently require sedation in order to produce ventilator-patient synchrony. Since ventilation is fully controlled, the patient is unable to compensate for acute changes in acid-base status or lung mechanics and is prone to alveolar hypoventilation or hyperventilation. Therefore, in essence, in this mode the physician assumes complete control of ventilation!

When properly used controlled ventilation can provide adequate ventilation and in addition can allow for recovery from respiratory muscle fatigue.

2. Assist Mode (Assist/Assist-Control) - In this mode, a positive pressure breath is delivered by the ventilator, triggered by the patient's effort. Therefore, the number of breaths per minute can be variable depending on the patient's demand. Different mechanisms have been designed which sense the patient's effort and trigger the ventilator. Some respond to changes in airway pressure either by displacing a diaphragm, thus creating an electrical signal, or by sensing pressure changes by means of transducers (e.g. Puritan-Bennett MA-I). Others respond to changes in flow produced by changes in airway pressure (e.g. Bourns Bear I).

With these systems, the amount of pressure or flow change needed to trigger a breath can be adjusted (sensitivity) making it easier (more sensitive) or harder (less sensitive) for the patient to receive a mechanical breath. In addition, the time elapsed from detection of the signal to the actual delivery of the ventilator breath can be variable depending on the ventilator being used. For example, the new Puritan-Bennett 7200 can sense patient effort in 20 milliseconds, whereas the older Puritan-Bennett MA-I is five times "slower" (100 milliseconds). When an automatic rate mechanism is combined with an assist one, a back up rate or level of ventilation is established which protects the patient in case he/she ceases to trigger the machine (assist-control).

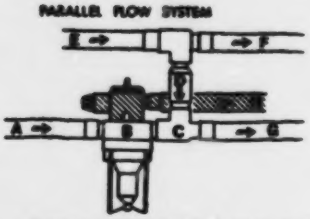
When the proper levels of sensitivity and inspiratory flow rate for a given level of minute ventilation are used, assist-control ventilation can increase patient comfort, improve ventilator synchrony, and reduce work of breathing. In contrast to controlled ventilation, patients on assist-control with normal neuromuscular function and chemoreceptor drive can respond to changes in acid-base status or lung mechanics by increasing or decreasing the level of minute ventilation. This not only serves to protect the patient, but also signals the physician that a change in clinical or metabolic status has occurred.

Intermittent Mandatory Ventilation (IMV/SIMV) - With this ventilatory mode spontaneous breathing is combined with a selected controlled mechanical rate. The tidal volume and rate of the spontaneous breaths are totally dependent on the patient's demand and performance. When provided in a synchronized fashion (SIMV) the mandatory ventilator breaths are patient assisted, avoiding superimposition of ventilator breaths over the patient's spontaneous breathing pattern. With IMV the patient is offered the physiologic advantage of maintaining a degree of spontaneous ventilation which may help to condition the muscles of respiration and improve venous return to the heart.

Most currently available ventilators incorporate IMV into their circuit. Older models can be modified in three general ways in order to provide this function: parallel flow, continuous flow, or demand valve (Figure 12). Knowledge about which type of IMV circuit is being used is important since the

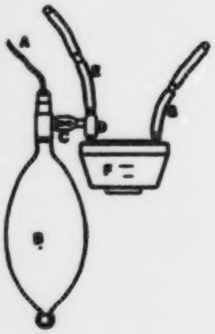
Figure 12.

Parallel Flow IMV



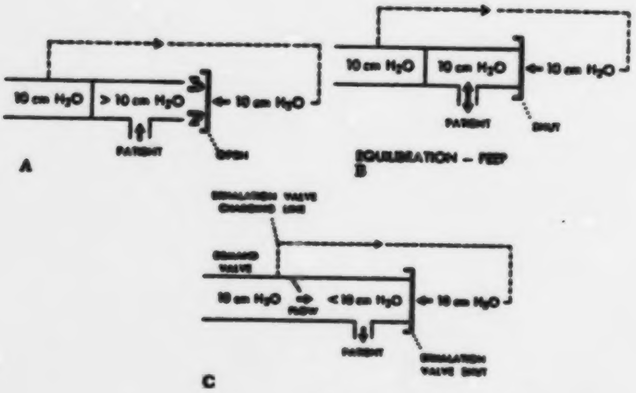
An open, parallel flow IMV circuit. (A) Gas flow from ventilator; (B) nebulizer; (C) t-piece; (D) unidirectional valve; (E) gas flow from external oxygen source; (F) end gas reservoir (open to ambient pressure); (G) inspiratory tube to patient; (H) expiratory limb from patient to exhalation valve. Spontaneous breathing occurs with gas flow from E and F. The patient must generate sufficient inspiratory effort to open the unidirectional valve, D. When the ventilator cycles, gas flow occurs from A→B→C→G and the valve, D, is closed.

Continuous Flow IMV



A closed, continuous flow IMV circuit. (A) Gas flow from oxygen blender; (B) reservoir bag; (C) unidirectional valve; (D) t-piece; (E) gas flow from ventilator; (F) humidifier; (G) gas flow to patient. Spontaneous ventilation draws gas flow from B. When the ventilator cycles, gas flow occurs from E→D→F→G and the unidirectional valve, C, is closed.

Demand-Flow Regulator IMV



(A) Beginning expiration: during exhalation the patient's expiratory flow increases the circuit pressure slightly above CPAP (e.g., >10 cm. H_2O). Sensing the increased pressure, the demand valve closes and the exhalation valve opens, venting excess pressure. (B) End expiration: when the patient's expiratory pressure equals the CPAP (e.g., 10 cm. H_2O), the exhalation valve closes, thereby maintaining the desired expiratory pressure. (C) Bird demand PEEP: a spontaneous inspiratory effort decreases the circuit pressure slightly below CPAP (e.g., < 10 cm. H_2O), causing the demand valve to open and providing gas flow to the patient.

amount of work performed by the patient in order to receive gas flow from these systems may vary considerably.

Pressure Support Ventilation (PSV) - With this mode, spontaneous breaths are supported by a constant amount of pressure. Airway pressure at the end of exhalation drops to 0cm H_2O (or to a preselected level of PEEP). Unlike volume assisted breaths, with PSV the patient sets the length of the inspiratory cycle and continues to receive support as long as he/she demands it (variable V_T).

The change from inspiration to expiration occurs when inspiratory flow falls below 25% of peak value (e.g., Seimens - Servo 900C). The concept is similar to that of IPPV with the advantage that it can be combined with controlled volume assisted breaths as in SIMV (SIMV + PSV).

The work performed by the respiratory muscles may be reduced in this low pressure, high volume setting as compared to the high pressure - low volume state of spontaneous ventilation in certain clinical conditions.

Special Techniques of Ventilatory Support

High Frequency Ventilation

This term encompasses at least three categories of ventilation defined on the basis of their frequency range, tidal volume and other operational characteristics.

High Frequency Jet Ventilation is the form most commonly used. A rate of 100-200 BPM and tidal volumes less than anatomic dead space are delivered to the patient. A high pressure jet, which may be constructed from a 14-18 gauge needle, pulses gas down the airways (Figure 13).

High Frequency Oscillation (HFO). With this mode a quickly moving piston produces very fast rates at volumes difficult to measure but which are certainly less than anatomic dead space (Figure 13).

High Frequency Positive Pressure Ventilation describes ventilation at frequencies between 60-110 BPM produced by specialized pneumatic devices which are incorporated in some available conventional ventilators.

The mechanisms by which alveolar ventilation is provided with HFV are not fully understood; however, gas transport most likely occurs by non-convective means (dispersive, diffusive, or coaxial flow mechanisms) with eventual mixing of gases in the airways. At lower rates (e.g.HFPPV), gas transport probably occurs by bulk flow as with conventional ventilation.

Although mean airway pressures are reduced with these forms of ventilation, alveolar pressures can increase significantly, particularly at fast rates.

High frequency ventilation may be useful in situations where large pulmonary air leaks occur (broncho-pleural fistula) and in providing ventilatory support during bronchoscopy or surgical procedures of the upper airway. To date, clinical studies have failed to show superiority of HFV over conventional ventilation with regards to complications and clinical outcome.

Extracorporeal Membrane Oxygenator (ECMO) - with ECMO, an artificial blood-gas exchange surface provides adequate O_2 and CO_2 transport. Technically it involves cannulation of a major vein and artery, anticoagulation, a pumping system and a membrane that functions as a "lung". Complications include hemodynamic instability, coagulopathies, and potential pulmonary vascular injury through the activation of complement.

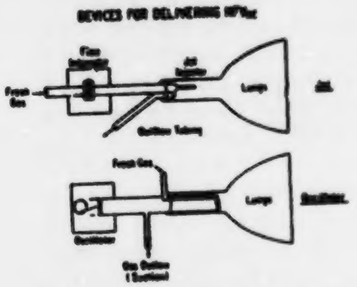
A large clinical study using ECMO in patients with severe acute respiratory failure failed to show improvement in mortality rates. Therefore, at the present time it is thought to have limited clinical utility in adults, although it may have a role in neonatal respiratory failure.

Differential Mechanical Ventilation - Occasionally patients develop severe unilateral lung disease which requires mechanical ventilation with high FiO_2's to maintain oxygenation. Usually these are cases of severe unilateral pneumonia with decreased pulmonary compliance and high shunt fraction as the main pathophysiologic derangement. In this situation, positive pressure ventilation, in particular PEEP therapy, can create significant hemodynamic instability and increase the likelihood of barotrauma since most of the positive pressure ventilation will tend to go to the lung with the higher compliance, i.e. the normal or less diseased lung. In addition transmission of high airway and alveolar pressures to the pulmonary vasculature can increase pulmonary vascular resistance, decrease blood flow, and cause redistribution of blood to the more diseased lung, potentially increasing shunt fraction. These changes will be more pronounced if PEEP therapy is used. In order to avoid these problems, selected patients with unilateral lung disease can be mechanically ventilated with two synchronized ventilators in a so-called "master-slave" arrangement.

After insertion of a double lumen endobronchial tube, tidal volume, FiO_2, PEEP and flow rates are selected for each lung based on their underlying pathophysiologic state. Some of the newly available ventilators can provide this function (Seimens-Servo 900C).

Table 5 summarizes the different modes of ventilatory support discussed.

Figure 13.



Devices for delivering HFV. Depicted are the two most commonly used ventilator principles for delivering ventilation at 2 to 30 Hz with $V_T < V_D$. A jet ventilator (top panel) periodically interrupts a high pressure gas source to produce pulses of gas through an injector in the airway. Exhalation is passive through an outflow channel. Jet characteristics may allow for entrainment of air to augment delivered volume. An oscillator (bottom panel) vibrates gas within the lungs. Fresh gas is added to the system from a bias flow and gas within the system is removed by a vacuum source.

Table 5.

Modes of mechanical ventilatory support.

Mode	Machine Control Over Rate	Machine Control Over Tidal Volume	Patient Control Over Rate	Patient Control Over Tidal Volume
Control	Yes	Yes	No	No
IMV	Yes (minimum)	Yes (mandatory volume)	Yes (can take unassisted spontaneous breaths)	Only with unassisted spontaneous breaths
Volume-Assist	Yes (backup)	Yes (minimum volume)	Yes (demand assisted breaths)	Can augment assisted volume through unassisted breathing circuit on some ventilators
SIMV	Yes (backup)	Yes (minimum volume)	Yes (demand assisted breaths and take unassisted spontaneous breaths)	Can augment assisted volume on some ventilators as well as determine the unassisted tidal volume
Pressure-Assist	No	Indirect through inspiratory pressure during demand period	Yes	Can determine tidal volume through interactions with inspiratory pressure
CPAP	No	No	Yes	Yes
Jet	Yes (60-150 BPM)	Yes, through interactions of jet pulse, entrainment source, and ventilatory system impedances	Can set a spontaneous rate along with jet rate	Can take unassisted tidal volume through unsupported breathing circuit

MECHANICAL VENTILATION: PHYSIOLOGIC CONSIDERATIONS

Over the past five years a great deal of interest has emerged regarding the role of the respiratory muscles in the pathogenesis of ventilatory failure. It has become apparent that respiratory muscle (especially diaphragmatic) fatigue and/or weakness contributes significantly to the development of ventilatory failure.

During normal ventilation less than 5% of the cardiac output is delivered to the respiratory muscles and their oxygen consumption is low. When the work of breathing is increased, the fraction of cardiac output delivered to these muscles can increase to as much as 20% and their oxygen consumption can exceed that of other critical organs. It is understandable then that respiratory muscle dysfunction can be precipitated or aggravated by conditions in which ventilatory demands are high and delivery of oxygen to the tissues is reduced, as in cardiogenic shock with pulmonary edema or any other low cardiac output state.

In patients with COPD it appears that hyperinflation alters the length/tension relationship of respiratory muscles leading to decreased force of contraction and poor muscle performance. This is compounded by the fact that these patients' work of breathing may be significantly increased secondary to their underlying lung pathology and abnormal pulmonary mechanics. It is thought that these patients are in a chronic state of respiratory muscle fatigue. Stresses that increase ventilatory demands may therefore increase their propensity to develop ventilatory failure.

Recent data suggest that mechanical ventilation, by decreasing the work of breathing, decreases oxygen consumption and the fraction of cardiac output delivered to these muscles. Ideally then, the preferred mode of ventilation should be one that at least initially provides a high level of mechanical support to allow for rest and recovery from muscle fatigue. A minimum of 48 hours of respiratory muscle rest may be needed to achieve this goal.

Conversely, it also appears that some degree of muscle work may be desirable in order to prevent muscle atrophy. How much work should be allowed, for how long and at what time, is not clear at this point.

What is the ventilatory mode of choice for patients with respiratory insufficiency?

Ideally it should be the one in which the patient performs the least amount of work. Two modes of ventilation offer this potentially important advantage; controlled ventilation and assist-control.

In the case of fully controlled ventilation, paralysis and sedation are usually required if the patient's work of breathing is to be eliminated or significantly reduced. Also as previously mentioned, in this mode the patient is unable to change his/her ventilatory requirements in response to metabolic needs. Therefore close monitoring of gas exchange is required, particularly in critically ill patients whose clinical and metabolic states are constantly changing. In spite of these disadvantages, controlled ventilation can be of utility in certain clinical settings.

Assist-control ventilation offers the patient with normal chemoreceptor and neuromuscular function the advantage of receiving a mechanical breath each time he desires as long as he is able to generate enough negative pressure or flow to trigger the ventilator. However, some words of caution regarding assist-control ventilation are appropriate at this time.

Marini, et al, have recently shown that in otherwise normal subjects, a significant amount of work can still be performed by the respiratory muscles when assist-control is used and that further increases in work can be produced when low flow rates and demand valve sensitivities are used. Therefore, assuming that patients ventilated in the assist mode are performing little work can be erroneous! Special attention should be given to inspiratory flow rates, to the type and sensitivities of demand valves and most important to physical findings suggestive of increased work of breathing (e.g. use of accessory muscles of respiration, etc.) If these factors are taken into consideration, it appears that the assist-control mode is the preferred and most physiological way to mechanically ventilate patients.

Should SIMV be used as a ventilatory mode? Most pulmonary and critical care clinicians interested in respiratory muscle physiology will agree that the role of SIMV as an initial choice of ventilatory mode is limited. However, it is probably unreasonable to assume that it has no role at all. Although its use may be of theoretical concern in situations where respiratory muscle dysfunction is present, it offers some potential advantages over controlled or assist-controlled ventilation (Table 6).

Table 6

PUTATIVE ADVANTAGES OF INTERMITTENT MANDATORY VENTILATION

1. Avoidance of respiratory alkalosis.
2. Minimal need for sedation to achieve ventilator synchrony.
3. Lower mean airway pressure.
4. More uniform intrapulmonary gas distribution.
5. Expedited weaning from mechanical ventilation.
6. Prevention of respiratory muscle atrophy or discoordination.
7. Reduced likelihood of cardiac decompensation during weaning from mechanical ventilation.

PUTATIVE DISADVANTAGES OF INTERMITTENT MANDATORY VENTILATION

1. Increased risk of CO_2 retention because IMV does not respond to increased ventilatory demand.
2. Increased work of breathing.
3. Respiratory muscle fatigue.
4. Prolonged weaning if IMV rate is decreased inappropriately slowly.
5. Increased likelihood of cardiac decompensation during weaning from mechanical ventilation.

It is currently unclear whether SIMV used in a synchronized fashion with pressure support ventilation (SIMV & PSV) is as good or better than control or assist control ventilation with regards to its effects on respiratory muscle function.

SIMV is frequently the ventilatory mode of choice when high levels of PEEP are required, since it allows for intermittent negative pleural pressure ventilation (i.e. spontaneous breathing). As a result mean airway pressure is lowered, possibly decreasing the risk of barotrauma and promoting cardiovascular stability.

As in the case of assist-control ventilation, a significant amount of work may be performed by the patient as he opens the one-way valve to receive gas flow from the IMV circuit. The amount of work performed will vary depending on the type of IMV circuit being used, the time-response and other characteristics of the demand valve and the rate of gas flow being delivered.

High frequency ventilation will not be discussed in further detail. The interested reader should read several excellent reviews.

Selection of Ventilatory Parameters

Once a ventilatory mode has been chosen, the next step is to select what respiratory rate, tidal volume, inspiratory flow rate, FiO_2 and PEEP (if indicated) will be used. In general, this is initially done empirically by selecting an initial FiO_2 of 100%, tidal volume of 10-15cc/kg, flow 40-60L/min, and rate anywhere from 10-15 BPM. Further adjustments are then made based on results of arterial blood gases obtained approximately 30 minutes later. These may reveal normal values for pH, p_aCO_2 and p_aO_2 or reveal abnormalities compatible with alveolar hypo- or hyperventilation with or without impairment of oxygenation.

With regard to alveolar hypo- or hyperventilation, it is important to remember that arterial pCO_2 is dependent on the amount of CO_2 produced (VCO_2) and the amount of CO_2 removed by alveolar ventilation. The effectiveness of alveolar ventilation can be assessed by measuring V_D/V_T which is an index of dead space or wasted ventilation. Therefore, hypercapnia seen in mechanically ventilated patients can be due to either disproportionate increases in CO_2 production in relation to the delivered minute ventilation (acidosis, fever, carbohydrate loads) or to increases in dead space ventilation (V_D/V_T), assuming minute ventilation has held constant. Some causes of an increased V_D/V_T include ventilation at fast rates with relatively low tidal volumes, pulmonary vascular disease, excessive ventilator tubing, and hypovolemia.

The minute ventilation required to obtain a desired pCO_2 can be calculated by the formula

$$\text{desired minute vent} = \text{Known minute vent} \times \frac{\text{PaCO2 (known)}}{\text{PaCO2 (desired)}}$$

This formula, however, is valid only if CO_2 production and dead space ventilation remain constant.

As previously mentioned, initially patients are placed on an FiO_2 of 100%. This is done because temporary hyperoxia is less damaging than temporary hypoxemia - the FiO_2 is subsequently reduced based on ABG results. Starting with an FiO_2 of 100% also allows one to quantify the degree of shunt. This can be done by means of the shunt equation

$$Q_S/Q_T = \frac{C_AO_2 - C_aO_2}{C_AO_2 - C_vO_2}$$

or by estimation (5% shunt for every 100 torr PaO_2 below 700), as long as PaO_2 is greater than 150 torr and the FiO_2 is 1.0. (Caution: 100% oxygen breathing can lead to resorption atelectasis, resulting in overestimation of degree of shunt present.)

The FiO_2 should then be lowered to levels which are not toxic to the lungs (<0.50) and which provide adequate oxygen delivery to tissues (Sat >90%). The FiO_2 needed to achieve a desired PaO_2 can be easily obtained by the following formula

$$\frac{700 \times \text{current } FiO_2}{\text{Measured } P_aO_2} = \frac{700 \times \text{new } FiO_2}{\text{Desired } P_aO_2}$$

If hypoxia persists in spite of FiO_2 >0.50 then PEEP is added unless contraindications to its use are present.

Termination of Mechanical Ventilatory Support

The great majority of patients who require mechanical ventilation can be successfully removed from the ventilator and extubated once the process responsible for their respiratory insufficiency resolves or significantly improves. The term "weaning" should be restricted to situations in which the patient becomes at least partially dependent on the ventilator, such that discontinuation of ventilatory support will need to be done in a gradual fashion.

Regardless of the clinical setting the following questions should be answered before attempting to terminate ventilatory support.

- Is the patient's overall clinical condition better or worse?
- Is the patient requiring FiO_2's >0.60 to maintain an adequate level of oxygenation?
- Can the patient meet certain pulmonary mechanics criteria which may successfully predict maintenance of spontaneous ventilation?

It would seem logical not to attempt withdrawal of mechanical support until the factors responsible for the patient's clinical condition have significantly improved or resolved, but it is surprising how often this mistake is made.

Inability to maintain adequate oxygenation in spite of high FiO_2's is suggestive of significant impairment of gas exchange and/or shunt. This may be a reflection of a new complicating process (pulmonary edema, etc) or persistence of the initial pathologic state, but in either case discontinuation of ventilation is impractical because the FiO_2 cannot be consistently maintained above 0.5-0.6 in the non-intubated patient.

Measurements of vital capacity, minute ventilation, and maximum inspiratory pressure can reflect on the underlying state of the "respiratory pump" (i.e. CNS, peripheral nervous system, chest bellows). Table 7 shows the parameters and values used in the prediction of weaning success.

Table 7

VALUES COMMONLY USED TO PREDICT WEANING SUCCESS

Measurement	Weaning attempt indicated
- Lung mechanics	
Vital capacity	> 10-15 ml/kg body weight
Minute ventilation V_E	< 10 L/min
Maximum voluntary ventilation	> 2 x resting $\dot{V}_E$
- Maximum inspiratory pressure	>-30cm H_2O
- Gas exchange	
V_D/V_T	< 0.6
$P(A-a)_{O_2}$, on 100% O_2	< 350 torr
Intrapulmonary right-to-left shunt	< 20%

These parameters should not be taken as independent predictors of weaning success but should be viewed as part of an overall assessment of the patient's clinical condition. Patients with normal neurologic function and adequate parameters whose clinical condition has improved can be successfully removed from mechanical ventilatory support in the great majority of cases. However, it is not uncommon to see patients who are successfully weaned in spite of suboptimal values for the parameters mentioned. In such cases, success may be due in part to the fact that the values measured may reflect poor patient cooperation and performance rather than significant abnormalities in pulmonary mechanics. In others the interaction of multiple factors play a significant role in determining which patients will be successfully weaned. These complicating factors are either of pulmonary or nonpulmonary etiology.

Dysfunction of any of the components comprising the pulmonary system can adversely affect the outcome of a weaning trial. These components are: central and peripheral nervous systems, the chest bellows, the airways and the alveoli.

Many factors can produce decreased level of consciousness in patients receiving mechanical ventilation. Some are shown in Table 8.

Table 8.

Various Factors Causing States of Altered or Decreased Consciousness in Patients Receiving Mechanical Ventilation.

Drugs
    Sedatives
    Analgesics

Metabolic and toxic factors
    Hypoxia, hypercapnia
    Acidosis, alkalosis
    Hyponatremia, hypernatremia
    Hypoglycemia, hyperglycemia with hyperosmolality
    Uremia, hepatic failure
    Postdialysis dysequilibrium syndrome
    Alcohol and drug withdrawal syndromes
    Bacterial sepsis

Structural central nervous system abnormalities
    Meningitis, other infections
    Strokes, subarachnoid hemorrhage
    Subdural hematoma
    Status epilepticus, postictal state
    Fat emboli

Other
    Sleep deprivation
    Intensive care unit or drug-induced psychosis

Changes in acid-base status can also have profound effects on ventilation. Both metabolic alkalosis and acidosis can alter central respiratory drive and interfere with weaning.

If serum bicarbonate concentration remains elevated for several days both CSF and blood will be alkalotic when pCO_2 is normal. When weaning is attempted, the central and peripheral chemoreceptors will not have the pH stimulus to maintain a normal or baseline pCO_2 and hypoventilation with hypercapnia will develop. In addition since serum bicarbonate is high, a lesser degree of acidosis will be produced per increase in pCO_2, decreasing the effectiveness of pCO_2 as a respiratory stimulant. This is of importance in patients with COPD with compensated respiratory acidosis and high serum bicarbonates. In these cases if the pCO_2 is lowered to less than baseline levels the serum bicarbonate may remain elevated if there is a concomitant metabolic alkalosis. Before weaning, attempts should be made to lower the serum bicarbonate to produce a slight respiratory acidosis at whatever pCO_2 is baseline for the patient. These can be done either by correcting the factors responsible for the alkalosis (see Table 9) or by the administration of the carbonic anhydrase inhibitor acetazolamide (Diamox).

Alkalosis (respiratory or metabolic) can also interfere with weaning by decreasing oxygen availability to tissues and by its adverse effects on myocardial performance (See Table 10).

Table 9

Causes of Metabolic Acid-Base Disturbances in Patients Receiving Mechanical Ventilation

Metabolic alkalosis (42):

- Causes
  - Contraction of extracellular space: diuretic use
  - Posthypercapnic state
  - Nasogastric suctioning
  - Hyperalimentation with exogenous loads of $NaHCO_3$, or alkalizing Na salts
- Maintenance
  - Decreased effective arterial volume
  - Potassium deficiency
  - Renal failure with reduced excretion of HCO_3^- loads
  - Hyperaldosterone state

Metabolic acidosis (29)

- Hyperchloremic
  - Gastrointestinal loss of HCO_3^-, diarrhea
  - Renal loss of HCO_3^-, acetazolamide, interstitial renal disease, renal tubular acidosis
  - Ureterosigmoidostomy
- Increased undetermined anion*
  - Generalized renal failure
  - Lactic acidosis
  - Ketoacidosis
  - Medication-associated salicylate intoxication

*Undetermined anion = (Na-) - (Cl-) + (HCO_3^-, with normal less than 12-14 meq/l.

Table 10

Physiological Effects of Respiratory Alkalemia (Hypocapnia)

Decreased

- Cardiac output
- Cerebral blood flow
- Coronary blood flow
- Lung compliance
- P_{50} (leftward shift O_2-hemoglobin dissociation curve - decreased oxygen availability)
- Serum ionized calcium
- Serum potassium

Increased

- Airway resistance
- Oxygen consumption

The patient with a metabolic acidosis and poor ventilatory reserve may not be able to provide respiratory compensation for the acid load. Nonetheless, the patient will be unavoidably "driven" by the stimulus of acidosis and will incur large increases in the work of breathing. Consequently, lactic acid produced by the fatigued respiratory muscles may aggravate the acidosis present.

Lastly an abnormal gag reflex, difficulty with swallowing, and cough may prevent extubation in patients who otherwise are ready to have mechanical ventilatory support discontinued.

As previously discussed, respiratory muscle weakness or fatigue can not only be the precipitating cause of ventilatory failure but can also hinder the weaning process. Respiratory muscle dysfunction in this setting can be due to either mechanical factors (e.g. inordinate work load secondary to airways obstruction, IMV circuits with high impedance, small diameter endotracheal tube), metabolic factors (hypokalemia, hypophosphatemia, hypomagnesemia), or atrophy (malnutrition, disuse secondary to prolonged mechanical rest).

Finally, persistent bronchospasm and secretions can further increase the work of breathing and predispose the patient to mucus plugging and hypoxemia.

Of the nonpulmonary factors, cardiovascular instability appears to be the most critical. Patients with low cardiac output, hypotension, or arrhythmias may have decreased O_2 delivery to the muscles of respiration at a time when metabolic demands are high. Low cardiac output can also increase dead space (V_D/V_T) in mechanically ventilated patients by creating high V/Q units. In addition, in patients with diseased lungs a low cardiac output can aggravate underlying hypoxemia by its effect in lowering mixed venous O_2 saturation in the presence of shunt.

Recently, investigators have developed a scoring system which takes into consideration some of the factors discussed plus others in an attempt to predict success in weaning. Although far from perfect, the value of such a system lies in the recognition of the multiple variables that can adversely affect weaning and which many times are overlooked by clinicians. (See Table 13)

Weaning is accomplished by one of two ways: T-tube trials with interposed periods of ventilatory support or by gradually decreasing IMV rates.

With the T-tube method, mechanical support is gradually decreased as periods of T-tube time are increased. During mechanical support the patient should ideally be placed on assist control in order to allow for recovery from muscle fatigue. When the patient is able to breathe unassisted for 2-3 hours the likelihood of success in weaning is good. Since FRC may decrease when mechanical breaths are withdrawn, as a general rule the FiO_2 is increased by 10% above baseline to avoid hypoxemia. Some patients require the addition of CPAP to maintain oxygenation.

With IMV, the number of ventilator breaths is progressively reduced until the patient no longer depends on the ventilator to maintain adequate gas exchange. IMV may offer the advantage of providing a graduated form of exercise for the respiratory muscles which may help to prevent disuse atrophy. However since the patient is expected to continuously provide part of the respiratory support, muscle fatigue and exhaustion can develop. This is particularly the case when the patient is left for a prolonged period on a low back up rate on a ventilator with an IMV system of high impedance characteristics.

Recent reports suggest that IMV combined with pressure support ventilation may decrease the work of breathing of patients being weaned from mechanical ventilatory support. Clinical studies are needed to compare this form of weaning with IMV and T-tube.

Table 11

Patient Monitoring During T-Piece Trial and Indications for Returning Patient to Ventilator

Type of Monitoring	Return to mechanical ventilator indicated
Clinical examination:	Diaphoresis Increasing respiratory distress, dyspnea Cyanosis Decreasing mental status Anginal pain
Physiologic parameters:	
ECG	New arrhythmias, ischemic changes
Heart rate	Tachycardia, bradycardia
Blood pressure	Hypertension, hypotension
Respiratory rate	> 35-40 breaths/minute
Minute ventilation	> 10 L/min
Arterial blood gases	
PaO_2	< 60 torr
$PaCO_2$	> 45 torr and rising
pH	< 7.26

Once the patient is placed on a T-tube or weaning is started with IMV, careful monitoring is required to detect clinical signs suggestive of poor ventilatory performance. Some of these parameters are shown in Table 11. If the patient performs poorly, he/she is placed back on the ventilator or his IMV rate is increased. Weaning is again attempted when conditions appear more favorable.

There is an emerging consensus among pulmonary physicians that T-tube weaning is the most effective method in patients with severe fatigue or derangement of pulmonary mechanics. Weaning from mechanical ventilation in conditions not complicated by respiratory muscle fatigue may be accomplished just as well by IMV weaning.

Respiratory Monitoring-Selected Aspects

Monitoring the mechanically ventilated patient can be a difficult and challenging task. These patients are frequently critically ill with multisystem organ dysfunction. Therefore careful attention is often required to assess the function of failing organ systems other than the lungs.

In general, monitoring techniques can be classified as either invasive or non-invasive. Of most relevance are those which can be performed at the bedside and which require equipment available in most ICU's. Table 12 shows some of the bedside parameters which are useful in following critically ill, mechanically ventilated patients.

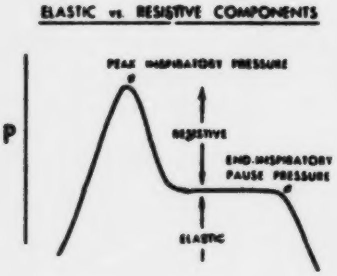
Table 12

Physical examination
Body weight
Urine output, plasma and urine osmolality, specific gravity, osmolar and free water-clearance
Radiological examination
Electrocardiogram (ECG)
Hematocrit and hemoglobin
Arterial blood gases
Intraarterial monitoring
Tidal volume (V_T), expired minute volume (V_E), and inspiratory force
Physiological dead space (V_D) or the ratio of dead space ventilation to total ventilation (V_D/V_T)
Bedside measurements of lung mechanics
Hemodynamic monitoring
Physiological shunt oxygen delivery
Inspired and expired gas measurements

The aim of respiratory monitoring should be to ensure that the best oxygenation and oxygen delivery to tissue are provided with the lowest airway pressures and FiO_2's, while maintaining cardiovascular stability.

1. Assessment of Pulmonary Mechanics

By sustaining inflation for 1-2 seconds it is possible to estimate the resistive and elastic components of the pulmonary system. The resistive component is roughly equivalent to the difference between peak airway pressure and end inspiratory pause pressure (Figure 14) and generally reflects the contribution of airways to total effective pulmonary compliance. The effective static compliance, which should reflect the elastic properties of the lung and chest wall, can then be calculated by dividing the delivered tidal volume by the difference between end inspiratory pause pressure (plateau pressure) and whatever positive pressure is present in the system at end expiration.

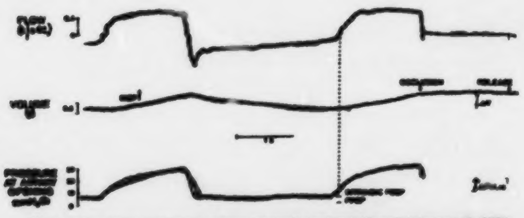


$$C^{st} = \frac{V^{T} - \text{amt. loss circuit}}{\text{Plateau pressure} - \text{PEEP}}$$

Rossi, et al, have recently shown that static pulmonary compliance can be underestimated by as much as 48% in patients in whom airway pressure at end exhalation is higher than that selected as PEEP (intrinsic PEEP). This situation is most likely to occur in patients with underlying airways obstruction being ventilated with low flow rates and short expiratory times. Therefore this pressure should be added to the externally applied PEEP whenever compliance measurements are to be made:

$$C^{st} = \frac{V^{T} - \text{amt. loss circuit}}{\text{Plateau pressure} - (\text{PEEP} + \text{intrinsic PEEP})}$$

Figure 15

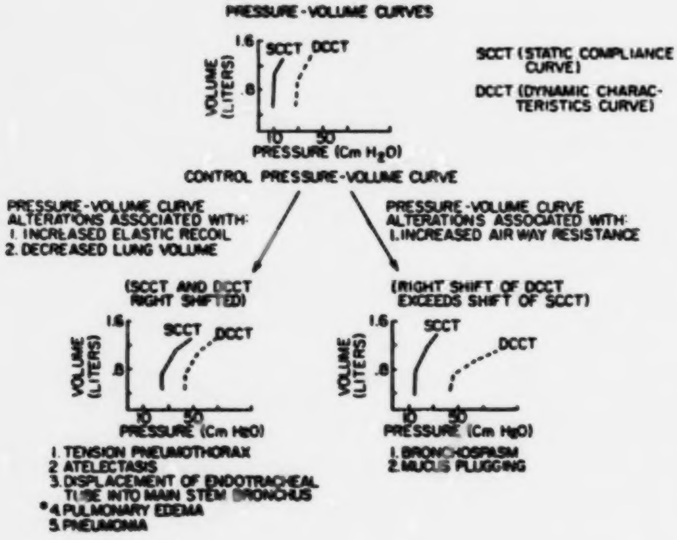


Tracing of flow, volume, and pressure at airway opening in a mechanically ventilated patient with COPD (Patient [illegible]) with PEEP of 3.5 cm H_2O. Arrows and symbols as in figure 1. Note that in this patient expiratory flow continues throughout expiration, and inspiratory flow starts only after a pressure change of +4.5 cm H_2O is applied by the ventilator, as indicated by the broken line. This pressure is required to overcome the end-expiratory elastic recoil, and is termed intrinsic PEEP. This figure illustrates the implications of intrinsic PEEP on measurement of $C_{st,rs}$. This is conventionally obtained as the ratio of inflation volume (ΔV) to the difference between the plateau end-inspiratory pressure and the PEEP set by the ventilator. Clearly, the end-expiratory elastic pressure of the respiratory system (i.e., the intrinsic PEEP) must also be subtracted from the end-inspiratory plateau in order to obtain the correct value of $\Delta P_{st,rs}$. In this example, uncorrected $C_{st,rs}$ amounted to [illegible] $L \cdot cmH_2O^{-1}$, whereas after correction for intrinsic PEEP the corresponding value was increased to [illegible] $L \cdot cmH_2O^{-1}$.

Figure 15 shows an example of intrinsic PEEP in a patient with COPD.

Normal effective static pulmonary compliance in ventilated patients is approximately 70-100ml/CM H_2O. By measuring dynamic and static compliances at different tidal volumes, pressure-volume curves are obtained which can be of utility in following the course of patients (see Figure 16). Pressure-volume curves may also be of help in determining the level of PEEP which gives the best compliance characteristics. This level is frequently variable and may be associated with the lowest dead space and maximal oxygen delivery.

Figure 16


PRESSURE-VOLUME CURVES
1.6
.8
VOLUME (LITERS)
SCCT
DCCT
10
50
PRESSURE (Cm H_2O)
CONTROL PRESSURE-VOLUME CURVE
SCCT (STATIC COMPLIANCE CURVE)
DCCT (DYNAMIC CHARACTERISTICS CURVE)
PRESSURE-VOLUME CURVE ALTERATIONS ASSOCIATED WITH:
1. INCREASED ELASTIC RECOIL
2. DECREASED LUNG VOLUME
PRESSURE-VOLUME CURVE ALTERATIONS ASSOCIATED WITH:
1. INCREASED AIR WAY RESISTANCE
(SCCT AND DCCT RIGHT SHIFTED)
(RIGHT SHIFT OF DCCT EXCEEDS SHIFT OF SCCT)
1.6
.8
VOLUME (LITERS)
SCCT
DCCT
10
50
PRESSURE (Cm H_2O)
1.6
.8
VOLUME (LITERS)
SCCT
DCCT
10
50
PRESSURE (Cm H_2O)
1. TENSION PNEUMOTHORAX
2. ATELECTASIS
3. DISPLACEMENT OF ENDOTRACHEAL TUBE INTO MAIN STEM BRONCHUS
*4. PULMONARY EDEMA
5. PNEUMONIA
1. BRONCHOSPASM
2. MUCUS PLUGGING

Another potential use of P-V curves is in the calculation of the work of breathing during mechanical ventilation. The work performed by the ventilator can be determined by measuring the area under a P-V curve when flow and tidal volume are kept constant. Estimation of work per breath may be of value as a way to monitor changes in respiratory impedance in ventilated patients.

2. PEEP

In 1975 the term "best PEEP" was introduced by Suter and Fairley to identify the level of PEEP that would maximize the beneficial effect of increasing FRC and reducing intrapulmonary shunting without producing a harmful effect on cardiovascular function. This level of PEEP was the setting at which the highest practical level of oxygen transport, mixed venous PO_2, and static compliance values, occurred together with the lowest reasonable dead space to tidal volume ratio. Since then the goals of PEEP therapy have remained the same. Cardiovascular stability is accomplished by monitoring hemodynamic parameters with a pulmonary artery flotation catheter. Oxygen delivery is assessed by measuring cardiac output, arterial oxygen content and mixed venous O_2 saturation.

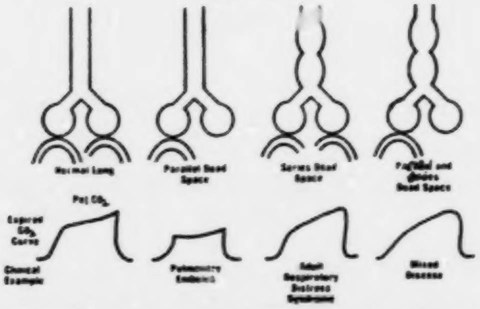
3. Physiological Dead Space (V_D/V_T)

This is the portion of tidal volume that does not participate in gas exchange and is normally about 150 ml (.2-.3 of tidal volume). V_D/V_T can be calculated by measuring arterial and mixed expired CO_2 tensions.

$$V_D/V_T = \frac{PaCO_2 - PECO_2}{PaCO_2}$$

As a rule, alveolar pCO_2 is assumed to equal arterial pCO_2. The exhaled gases are usually measured by either mass spectrometry or CO_2 analyzers which are available in many ICU's today. Figure 17 shows a graphic representation of clinical settings in which V_D/V_T is increased and when serial measurements may be of clinical utility. The relationship between V_D/V_T and PCO_2 was discussed in a previous section.

Figure 17



Physiological dead space can be increased by diseases causing ventilation that exceeds perfusion. Graphic representation of diseases producing increased dead space and the resulting expired carbon dioxide curve is shown. (Reprinted with permission from Bone RC: Monitoring patients in acute respiratory failure. Respir Care 27:700, 1982.)

Lastly, by means of continuous monitoring of both inhaled and exhaled gases, the course of many patients can be closely followed in many of our modern ICU's. Variables such as FiO_2, flows, V_D/V_T, $\dot{V}_{O_2}$ (O_2 consumption), O_2 delivery, peak airway pressures and others, can be continuously recorded by computers. Recording of this information may be of value in the detection of changes in the patient's clinical status or of mechanical problems like E-T tube air leaks or ventilator malfunction.

Whether monitoring of all these variables and its associated costs (mass spectrometer, etc) will have an impact on patient outcome remains to be seen.

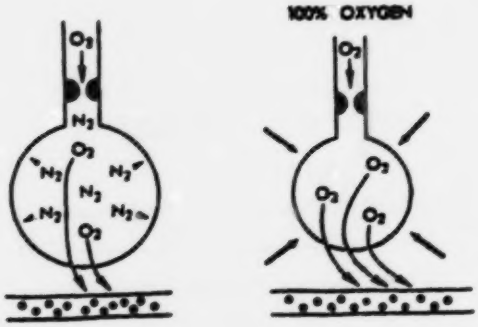
COMPLICATIONS OF MECHANICAL VENTILATION

Oxygen Therapy Hazards of oxygen therapy include retrolental fibroplasia and bronchopulmonary dysplasia in the premature and newborn, CO_2 retention in COPD patients (depending on their hypoxemic ventilatory drive), absorption atelectasis, and pulmonary oxygen toxicity. Some of these problems are discussed below.

1. CO_2 retention may be exacerbated in a few patients with severe COPD with chronic CO_2 retention compensated by elevated bicarbonate levels. These patients depend upon their hypoxemic ventilatory drive, which when taken away by the administration of high FiO_2's may result in further ventilatory depression and further CO_2 retention and narcosis. Concern over ventilatory depression should never prevent oxygen administration for the relief of severe hypoxemia (PaO_2 less than 50 torr).

2. Absorption atelectasis occurs when breathing oxygen at concentrations greater than 60 percent washes out alveolar nitrogen from marginally ventilated but still perfused alveoli. When the alveolar oxygen is taken up by the pulmonary capillary blood in excess of that resupplied to the alveoli by ventilation, collapse occurs (see Figure 18).

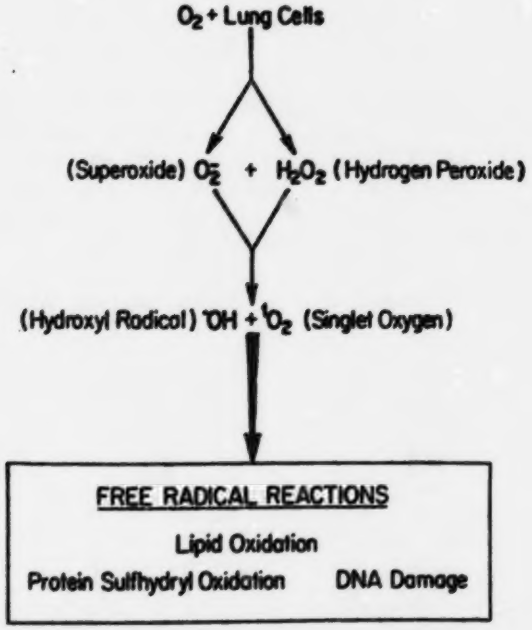
Figure 18. Mechanism of Adsorption Atelectasis



Whenever possible FiO_2 should be limited to less than 0.6 in spontaneously breathing patients to prevent the conversion of these low V/Q areas to shunt units. PEEP may minimize this iatrogenic complication in the mechanically ventilated patient.

3. Pulmonary oxygen toxicity was classically described by J. Lorrain Smith in 1899. It is well established that exposure to high partial pressures of oxygen for prolonged periods can produce serious and even lethal damage to the lungs. Structural alterations include the formation of fibrin membranes, alveolar and septal thickening, endothelial destruction, and an initial small decrease in Type I pneumocytes followed by a progressive proliferation of Type II pneumocytes. Other pulmonary effects include depression of alveolar macrophage bacterial killing, mucociliary clearance, diffusion capacity, pulmonary compliance, and increased airway resistance. It is unlikely that toxicity occurs in man at FiO_2's less than 0.5 at 1 ATA even with prolonged exposure except when there has been recent prior or concurrent exposure to hyperbaric oxygen tensions, recent radiation to the lung, or use of certain chemotherapeutic agents (e.g. Bleomycin). Oxygen radicals produced by single electron transfer are thought to be responsible for the cellular damage produced (Figure 19).

Figure 19


O_2 + Lung Cells
(Superoxide) O_2^- + H_2O_2 (Hydrogen Peroxide)
(Hydroxyl Radical) $\cdot OH$ + $^1O_2$ (Singlet Oxygen)
FREE RADICAL REACTIONS
Lipid Oxidation
Protein Sulfhydryl Oxidation
DNA Damage

Chemical Mechanisms of Oxygen Toxicity.

Nosocomial pulmonary and systemic infections are an ever present hazard in respiratory failure patients due to contamination from respiratory therapy equipment, invasive monitoring devices and contact with hospital personnel. These risks can be minimized by careful attention to infection surveillance, handwashing, aseptic techniques for line placement, and changes of ventilator circuits and humidifier/nebulizers.

Specific hazards of positive airway pressure therapy

1. Cardiovascular compromise occurs as cardiac output falls in response to increasing mean airway pressure. The reduction in cardiac output correlates directly with the decrease in transmural right ventricular filling pressure as intrapleural pressure rises. This change in intrapleural pressure is dependent on airway pressure and lung and chest wall compliance. The incidence of cardiovascular depression is also correlated with intravascular volume. Therefore the adverse hemodynamic effects of IPPV (and PEEP) can be decreased with adequate intravascular volume support and occasionally with the addition of inotropic agents.

PEEP can also decrease cardiac output by increasing pulmonary vascular resistance due to transmission of high alveolar pressures to the pulmonary circulation. This can produce right ventricular dysfunction, and decreased left ventricular compliance. The dilated RV can cause the interventricular septum to bulge into the left side during systole (ventricular interdependence). However, like any type of positive pressure ventilation, the main mechanism by which PEEP decreases cardiac output is by decreasing venous return to the heart. Table 14 lists the hemodynamic effects of PEEP therapy.

Table 14

CARDIOVASCULAR EFFECTS OF PEEP

Causes	Proposed Mechanisms
Reduced Cardiac Output	
Primary reduction in venous return	Increased intrathoracic pressure resulting in increased lung and intrapleural pressures Elevated right atrial pressure reduces mean circulatory pressure Compliant lung regions predominate Loss of peripheral sympathetic tone
Increased pulmonary vascular resistance	Increased alveolar pressure
Right ventricular failure	Pulmonary hypertension Inadequate intravascular volume Release of negative inotropic agents
Left ventricular failure	Right ventricular failure (ventricular interference) Subendocardial ischemia Release of negative inotropic agent Reflex depression due to stimulation of neural receptors
Increased (or stable) Cardiac Output	
Uniformly noncompliant lung or high airway resistance	Decreased transmission of airway pressure
Correction of low FRC	Improved pulmonary perfusion perfusion with reduced pulmonary vascular resistance
Correction of hypoxemia	Lowering of pulmonary vascular resistance Improved myocardial efficiency
Left ventricular failure	Reduction of left ventricular afterload and more efficient ventricular emptying
Volume expansion (hypervolemia)	Increased ventricular filling pressures

2. Pulmonary barotrauma refers to damage produced by excessive airway pressures. Positive airway pressure may produce alveolar rupture leading to the development of pulmonary interstitial emphysema (PIE), culminating in subcutaneous emphysema, pneumothorax, pneumomediastinum, or pneumoperitoneum. The caliber of the pulmonary blood vessels in part determines the pressure gradient between the alveolus and the perivascular sheath. Intravascular volume expansion may protect against barotrauma by maintaining pulmonary vascular filling.

3. PEEP may also increase extravascular, interstitial lung water. Four mechanisms have been implicated: partial obstruction of pulmonary lymph flow, increased pulmonary microvascular permeability, decreased interstitial fluid pressure around exchange vessels, and increased surface area of exchange vessels.

4. PEEP therapy may reduce hepatic, adrenal, bronchial, gastric, coronary, and subendocardial blood flow.

5. PEEP may increase cerebral venous and intracranial pressure by impeding thoracic venous return. Increases in ICP are roughly proportional to the increments in PEEP. Increases, however, do not occur in all patients (< 50%).

6. Positive pressure ventilation can cause decreased sodium excretion, fluid retention, and decreased urine output. Decrease in free water clearance secondary to ADH release, and changes in intrarenal perfusion with decreases in mean renal arterial pressure and perfusion of the renal cortex probably account for these effects.

Table 15 lists some other complications of mechanical ventilation.

Table 15

Complications Observed Prospectively

A. Complications attributable to intubation and extubation

1. Prolonged attempt at intubation
2. Intubation of right mainstem bronchus
3. Premature extubation
4. Self-extubation

B. Complications associated with endotracheal/tracheostomy tubes

1. Tube malfunction
2. Nasal necrosis

C. Complications attributable to operation of the ventilator

1. Machine failure
2. Alarm failure
3. Alarm found off
4. Inadequate nebulization or humidification
5. Overloading or inspired air

D. Medical complications occurring during assisted ventilation

1. Alveolar hypoventilation
2. Alveolar hyperventilation
3. Massive gastric distention
4. Pneumothorax
5. Atelectasis
6. Pneumonia
7. Hypotension

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CONGENITAL LUNG DISEASE

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The topic of congenital lung disease covers a diverse group of pulmonary anomalies ranging from developmental anomalies to genetic disorders of the respiratory tract. This discussion is directed towards developmental anomalies which may become first manifest during adulthood. It also includes a brief description of the embryological evolution of the lungs.

Developmental anomalies of the lungs are typically classified into one of two groups based upon the predominant tissue form affected. Abnormalities of the primitive foregut or its derivative, the lung bud, are referred to as bronchopulmonary foregut anomalies. Foregut anomalies to be discussed include pulmonary agenesis, aplasia, and hypoplasia, bronchial anomalies, bronchogenic cysts and bronchopulmonary sequestration. The second class of malformations are those of the pulmonary vasculature which arise during development of the sixth embryonic arch. The discussion of the vascular anomalies will be limited to the two conditions of arteriovenous malformations and the syndrome of anomalous pulmonary venous drainage or scimitar syndrome.

Embryologically the primordium of the respiratory tract first appears when the embryo is 21 to 22 days old. The normal developmental sequence of the lower respiratory tract may be divided into four periods. The embryonic period begins at conception and lasts to the eighth week. During this period, the embryonic endoderm gives rise to the foregut. On day 22, the foregut gives rise to the esophagus and the respiratory tract with the formation of a median pharyngeal groove. The lung bud primordium becomes apparent at this stage. The lung bud grows in a caudal direction forming the trachea and soon bifurcates into the bronchi. The lung buds (bronchi) are enveloped by the splanchnic mesoderm which eventually gives rise to the bronchial musculature, the cartilaginous rings, the visceral pleura, and the pulmonary capillary plexus. During the seventh week the truncus arteriosus separates into the aorta and the pulmonary artery. The pulmonary artery also fuses with the pulmonary plexus (1). Weeks eight through sixteen are known as the pseudoglandular period. During this time the bronchial diversions establish and proliferate. The canalicular period is from four months to six months. This time interval is associated with respiratory bronchiolar development and mature alveolar cells begin to appear. At six months the embryo enters the terminal sac period. At this time, definite capillary loops form and type 1 and type 2 pneumocytes appear. By the seventh month, the alveolar system can support extrauterine respiration. After birth, the number of terminal alveoli increase ninefold. This increase occurs primarily during the first year of life, but continues up to age 12 (2). The latter finding supports the concept that the tracheobronchial tree is formed as a diverticulum from the foregut. Another proposed theory is that of esophagotracheal septation; according to this theory the respiratory diverticulum is initially in wide open communication with the foregut until an esophagotracheal septum forms. This theory best explains tracheoesophageal fistula formation (2). Actually, it is exceedingly difficult to explain all the known congenital pulmonary anomalies by any one theory.

BRONCHOPULMONARY FOREGUT ANOMALIES

Pulmonary Agenesis, Aplasia, and Hypoplasia

Pulmonary agenesis is a rare anomaly defined as the complete absence of one or both lungs with no histological evidence of bronchi, pulmonary parenchyma or vascular supply. Pulmonary aplasia on the other hand is associated with suppression of all development other than a residual rudimentary bronchus which ends in a blind pouch. Both conditions, dependent upon severity and associated congenital anomalies, may be asymptomatic (3). With unilateral involvement, which is the most frequent form, radiographic findings include hyperinflation of the remaining lung with contralateral mediastinal shift. Sixty percent of patients with agenesis have associated congenital abnormalities including PDA, tetralogy of Fallot, bronchogenic cysts and congenital diaphragmatic defects. Right pulmonary agenesis is associated with a higher incidence of associated anomalies. The most common complication of these conditions, especially pulmonary aplasia, occurs when the pooling of secretions in the blind bronchial stump results in "spillage pneumonitis" (3). Pulmonary hypoplasia is another rare anomaly. It has an incidence of 1 in 10,000 with no associated sexual predominance. In this condition, the bronchus is completely formed with associated rudimentary pulmonary parenchyma. It most commonly involves a whole lung, however it may involve only a single lobe. It is associated with anomalous pulmonary arterial supply and venous drainage. At times, its etiology has been attributed to in utero decreased intrathoracic space. Factors resulting in pulmonary agenesis, aplasia and hypoplasia must occur between the twenty-second day and sixth week of embryological development.

Bronchial anomalies

Figure 1 demonstrates several possible bronchial anomalies. Tracheal diverticuli and tracheal bronchi are the result of abnormal bifurcation of the lung bud during the embryonic period. A tracheal diverticulum normally originates from the cervical trachea and ends blindly or in a rudimentary lung. A tracheal bronchus may connect to an apical segment of the upper lobe, most often the right upper lobe, or to an isolated intrathoracic segment. Rarely an anomalous bronchus may communicate with other derivatives of the foregut such as the esophagus or the biliary tree. In this case, the abnormalities are most frequently found on the right side and are associated with an aberrantly derived blood supply (2).

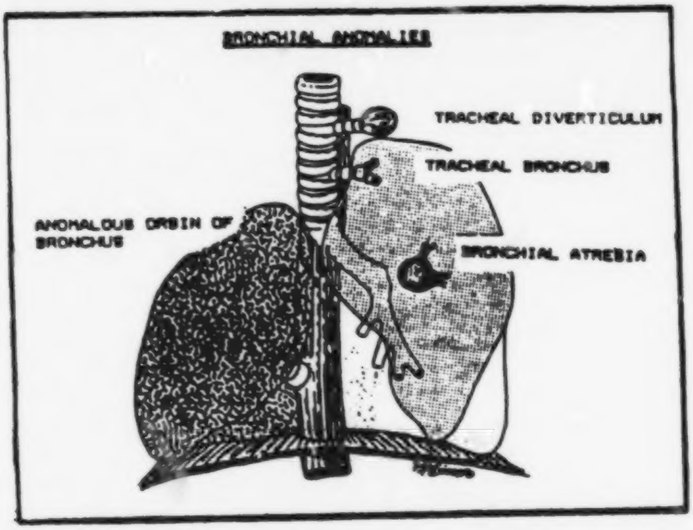

FIGURE 1

Bronchial atresia is an interesting but uncommon congenital anomaly which typically presents in young adults as an incidental finding on screening radiographs. Radiographically the anomaly presents as an extrahilar mass with associated peripheral hyperinflation. Characteristically the patient is in the second decade of life and is asymptomatic. The most frequent location is the left upper lobe. Segmental involvement is most common, but lobar atresias have been reported (5). Pathologically, bronchial continuity is interrupted in the embryonic period, resulting in an isolated distal bronchial segment. Often rudimentary connections between the distal segment (mucocele) and proximal bronchus may be found. The isolated bronchial segment becomes a mucus filled cyst with "fingerlike projections" into the parenchyma. The mucocele is lined with normal respiratory epithelium. The parenchyma distal to the atretic bronchus may receive collateral ventilation by the pores of Kohn and thus become hyperinflated. Embryologically the anomaly is felt to result from a vascular insult during the embryonic period which results in an atretic proximal bronchial segment with a distally normal bronchus. Characteristic findings include the following. (1) Bronchography reveals nonfilling of the bronchial segment and displacement of the neighboring bronchi secondary to hyperinflation. (2) Tomography may reveal the mucocele with its fingerlike projections. (3) Angiography reveals normal or decreased vascularity in the atretic segment. (4) Bronchoscopy may demonstrate an absent bronchial segment. Rarely, surgery may be indicated to confirm the diagnosis. The treatment of bronchial atresia is controversial, though most authors feel surgical excision, even prophylactically, is indicated to prevent the complications of hyperinflation and infection of the mucocele (5).

Bronchogenic Cysts

Bronchogenic cysts are rare anomalies which occur when a segment is "pinched off" the normal lung bud and becomes separated from the normally developing tracheobronchial tree. They originate before the bronchi are formed and normally do not communicate with the bronchial tree. They tend to occur more frequently in males than females. Bronchogenic cysts present in early life or adulthood as incidental radiographic findings, with chronic infectious complications, or as a result of respiratory symptoms secondary to extrinsic bronchial compression (6). Often congenital bronchogenic cysts are classified into two groups: (1) pulmonary or parenchymal cysts, and (2) mediastinal cysts. Parenchymal cysts are most often found in the lower lobes (right > left) and often present with infectious complications. Other presenting symptoms may include hemoptysis, space-occupying problems, and rarely pneumothorax. Mediastinal cysts have been classified by Mair according to their location: (1) paratracheal, (2) carinal, (3) hilar, (4) paraesophageal, and (5) miscellaneous. The majority of mediastinal cysts are located near the carina and are attached to the main airways by a nonfunctioning stalk. Clinically patients present with symptoms of extrinsic airway compression or more rarely with dysphagia (7).

Pathologically, the cysts are lined with ciliated columnar or cuboidal epithelium; fragments of cartilage and smooth muscle are present in their walls. Radiographically they appear as smooth ovoid and sharply circumscribed opacities. Air-fluid levels may be present, or they may be completely radiopaque, either filled with secretions or pus. Bronchoscopy may be used to rule out proximal obstruction. CT scanning is the best available diagnostic tool. Cysts derive their vascular supply from either small systemic arteries or the pulmonary artery and angiography is not routinely indicated. Most authors recommend excision of the cysts, even if asymptomatic, as the majority (75%) will become secondarily infected (4).

Bronchopulmonary Sequestration

Bronchopulmonary sequestration is an uncommon, though not rare, manifestation of a bronchopulmonary foregut malformation. The anomaly is characteristically a non-functioning pulmonary lobe or segment which does not communicate with the normal bronchial tree or trachea. It derives its blood supply from an aberrant systemic artery. Sequestrations are referred to as intralobar if the abnormal pulmonary tissue is incorporated into the normal lung and shares a common covering of visceral pleura. In extralobar sequestrations, the abnormal pulmonary tissue is separated from the normal lung, with its own pleural investment. (8) Extralobar sequestrations are also referred to as accessory lobes or Rokitansky lobes. (2) Savic and associates reviewed 540 cases of lung sequestration and noted the anomaly comprises 0.15 to 6.4% of all congenital lung disease (9). Its reported overall frequency in one surgical series was 1 case per 1,051 adults undergoing pulmonary resection for another reason. Intralobar sequestration is 6 times more common than the extralobar form. The condition is most frequently diagnosed in young adults and is more common in men than women. Reported male:female ratios are typically 1.5:1.0 for intralobar sequestration and 3.0 to 1.0 for extralobar sequestration. (11) This discussion will focus on the etiologic theories concerning lung sequestration, the characteristics of both intralobar and extralobar forms and finally diagnostic and therapeutic interventions.

Since its initial description in 1861, multiple theories have been proposed to explain the origin of sequestrations. Boyden proposed that they result from the coincidental occurrence of both aberrant systemic arteries to the lung and cystic lung lesions (10). Smith hypothesized that localized pulmonary artery insufficiency resulted in the persistence of a primitive systemic arterial blood supply. He proposed the degenerative vascular and parenchymal changes associated with sequestration resulted from the prolonged exposure of the pulmonary parenchyma to systemic arterial blood pressures. (11) Along somewhat similar lines of reasoning, Pryee proposed a "traction theory" to explain the anomaly. According to this line of reasoning, the primary anomaly is a vascular malformation with the persistence of an aberrant artery arising from the systemic circulation. The aberrant artery creates a traction force on the normal bronchial tree, with the cystic changes resulting from injuries to the parenchymal tissue. (11) Currently, the most widely accepted theory of sequestration development is the idea of an accessory lung bud which is formed early on during the embryonic stage. Gerle and associates feel this theory best explains both intralobar and extralobar sequestration. According to this hypothesis, an accessory lung bud forms during the embryonic stage distal to the normal lung bud. As previously mentioned, both are derived from the primitive foregut. The accessory bud derives its blood supply from the splanchnic plexus. The time at which the accessory lung bud forms determines whether it results in an intralobar sequestration (early) or an extralobar sequestration (late). If developmental arrest occurs early on during the development of a sequestration, the sequestered segment may remain in communication with the GI tract, usually at the level of the esophagus or cardioesophageal junction. (8) Lastly, Gebauer and Mason proposed that pulmonary sequestration is not a congenital disease but rather an acquired process whereby the primary lesion is an infection in the pulmonary parenchyma with resultant chronic inflammation. The presence of a chronic inflammatory focus then stimulates the hypertrophy of bronchial and mediastinal arteries which form the systemic arterial blood supply to the lesion.

As mentioned earlier, intralobar sequestration is the most common form of pulmonary sequestration and represents 5 to 6% of all congenital lung disease. Clinically, patients most commonly present with a history of recurrent bronchitis, pneumonia, bronchiectasis and occasionally with hemothorax or hemoptysis. Four percent of patients present with pleurisy and pleural effusion. Rarely, usually in infants, patients may present with evidence of congestive failure. Savic reported that 37% of patients present within the first decade of life and 20% during the second decade; 15% present with an abnormal radiograph without any prior symptoms. (9) Radiographically the sequestered segment most commonly presents with multiple air-fluid levels, cystic regions or as a homogeneous shadow. On Savic's review of 400 cases of intralobar sequestration reported in the literature, he noted greater than 95% of the sequestered regions were in the lower lobes, left being more common than right. (See Figure 2) There has been one reported case of bilateral intralobar sequestration. (8) The arterial supply of a sequestered segment typically reaches the segment via the inferior pulmonary ligament. Histologically the vessels appear to be of an elastic type (pulmonary type) as opposed to the normal muscular type seen in systemic vessels. Over 75% of the patients present with premature atherosclerotic changes and intimal thickening. (8) The mean arterial diameter of the vessels ranges from 6.3mm to 6.6mm. (9) As seen in Figure 3, the majority of sequestered segments derive their arterial blood supply from the descending thoracic aorta. (9) Fifteen percent of all sequestered segments derive their blood supply from multiple aberrant arteries which may originate from both above and below the diaphragm. (8) The venous drainage of intralobar sequestrations is more uniform with 95.7% of the segments being drained via the pulmonary veins and 4.3% via the systemic veins. (9) Thus most of these patients have a left-to-left shunt of varying portions. Approximately 14% of patients have other associated congenital anomalies including esophageal diverticuli, diaphragmatic hernias, skeletal deformities and congenital heart disease. At the time of surgery, two histological groups can be recognized. The most common histological finding is a cystic-bronchiectatic form which may be further subdivided into three subgroups: 1) solitary cystic form, 2) polycystic form, and 3) mixed cystic form. An unusual histological finding is the pseudotumorous form. These patients typically present with no clinical findings or complaints. (9)

INTRALOBAR SEQUESTRATION

RADIOGRAPHIC FINDINGS

- MULTIPLE AIRFLUID LEVELS, CYSTIC REGIONS, HOMOGENOUS OR NONHOMOGENOUS SHADOWS
- SAVIC'S REVIEW OF 400 PATIENTS NOTED THE FOLLOWING LOCATIONS:
    - LLL....................56.7 %
    - RLL....................41.0 %
    - UPPER OR MIDDLE LOBES........2.3 %

FIGURE 2

ARTERIAL BLOOD SUPPLY TO
INTRALOBAR SEQUESTRATIONS

SITE	FREQUENCY
DESCENDING THORACIC AORTA	74 %
ABDOMINAL AORTA	18 %
INTERCOSTAL ARTERIES	3 %
SUBCLAVIAN ARTERY	<1 %
INTERNAL THORACIC ARTERY	<1 %
CELIAC ARTERY	<1 %

FIGURE 3

Extralobar sequestration is much less common than the intralobar form and represents less than 1% of all congenital lung disease. In contrast to intralobar sequestration, patients with extralobar sequestration seldom present with symptoms related to the anomaly; typically the abnormality is noted as an incidental finding on radiographs or is discovered at the time of operative repair of a Bochdalek diaphragmatic hernia. Rarely the patient, usually an infant, may present with CHF as a result of the left-to-right shunt. Radiographically the anomaly most frequently appears as a triangular shaped density in the posterior costophrenic angle adjacent to the esophagus or aorta. As seen in Figure 4, the majority of the lesions (77.4%) are found in the basilar segments, however extralobar sequestrations may be found in more diverse locations than the intralobar variety. (9)

LOCATION OF EXTRALOBAR SEQUESTRATIONS
(n = 133)

LOCATION	FREQUENCY
BASILAR SEGMENTS	77.4 %
- RIGHT	(13 %)
- LEFT	(64.4 %)
ABDOMINAL	8.2 %
MEDIASTINUM	4.1 %
BETWEEN UPPER AND LOWER LOBES	4.1 %
PERICARDIAL	2.2 %
OTHER	3.4 %

FIGURE 4

ARTERIAL BLOOD SUPPLY TO
EXTRALOBAR SEQUESTRATIONS

SITE	FREQUENCY
DESCENDING THORACIC AORTA	46.1 %
ABDOMINAL AORTA	31.6 %
INTERCOSTAL ARTERIES	6.6 %
PULMONARY ARTERY	5.5 %
CELIAC ARTERY	1.0 %
GASTRIC ARTERY	2.2 %
ASCENDING THORACIC AORTA	1.0 %
RENAL ARTERY	1.0 %
OTHER	7.2 %

FIGURE 5

Like the intralobar form, arteries supplying an extralobar sequestration are predominantly of the elastic type. Up to 20% of extralobar sequestrations receive their systemic arterial blood supply from multiple aberrant arteries. The most common origin of the arterial blood supply is the descending thoracic aorta (46.1%) with the second most common site of origin being the abdominal aorta. Other less common sites of origin may be found in Figure 5. The venous drainage of an extralobar segment is into the systemic venous circulation via the azygos, hemiazygos, or portal veins. Only rarely will the venous drainage empty into the pulmonary vein. Therefore, extralobar sequestrations usually result in a left-to-right shunt. Extralobar sequestrations are associated with an increased incidence of other congenital anomalies, with up to 58% of patients having a second congenital defect. The most common associated congenital anomalies are diaphragmatic hernia (28%) and diaphragmatic eventration (12). It is felt these defects may be more common because the anomalous sequestered segment may interfere with the closure of the pleuroperitoneal canal. (8) Other associated congenital anomalies are found in Figure 6. At the time of surgery, histological examination of an extralobar sequestered segment reveals atelectatic, embryonal, and partially dysplastic lung tissue.

CONGENITAL ANOMALIES ASSOCIATED WITH
EXTRALOBAR SEQUESTRATIONS

ANOMALY	FREQUENCY
CONGENITAL DIAPHRAGMATIC HERNIA	28 %
EVENTRATION OF DIAPHRAGM	14 %
PAVMs AND OTHER LUNG ANOMALIES	3 %
FOREGUT DUPLICATION	2.2 %
CONGENITAL MEGACOLON	0.7 %
PECTUS EXCAVATUM	
PERICARDIAL CYSTS	
CONGENITAL ABSENCE OF PERICARDIUM	

FIGURE 6

The diagnostic approach to both intralobar and extralobar sequestrations is similar in that the primary objective is to define the presence of a systemic arterial supply and to identify its origin. Non-invasive diagnostic studies include: 1) tomography which may demonstrate the absence of bronchial connections, but rarely identifies an aberrant artery; 2) nuclear angiograms, the use of which has not been well delineated at this time; and 3) CT scanning (dynamic) which has a reportedly good diagnostic sensitivity in establishing the presence of systemic arterial blood supply and may identify the feeding artery. Angiography is considered the "gold standard" in establishing the arterial supply and venous drainage of a sequestered segment. Most authorities insist that an angiogram be performed prior to any surgical intervention to identify the vascular anatomy. The most common cause of death at the time of surgery is exsanguinating hemorrhage, from the inadvertent transection of an aberrant artery which then retracts into the mediastinum or below the diaphragm and is not easily relocated. Bronchography is usually not helpful in establishing a diagnosis of sequestration. Typical findings at bronchography include a normal complement of bronchi with displacement of the terminal bronchial branches by a space-occupying lesion. Intralobar sequestration communicates with the normal bronchial tree in 17% of cases by a fistulous communication. Extralobar sequestration rarely communicates with the bronchial tree. Bronchoscopy is usually non-revealing except to rule out a proximal endobronchial obstruction. Upper GI studies should be performed in all patients with suspected sequestration to rule out a fistulous communication between the GI tract and the sequestered segment forming an "esophageal lung." The only available treatment for symptomatic intralobar and extralobar sequestration is surgical excision. The only exception to this would be cases in which significant hemodynamic compromise from left-to-right or left-to-left shunt may be treated by ligation of the systemic arterial blood supply. Asymptomatic extralobar sequestration does not require surgical resection. On the other hand, controversy exists as to whether asymptomatic intralobar sequestrations should be removed prophylactically. The removal of a previously infected intralobar sequestration may be technically difficult as the surgical planes are difficult to define in the presence of chronic inflammatory changes. In Savic's review of 319 patients undergoing thoracotomy for an intralobar sequestration (most of them infected), lobectomy was required in 71.5% of cases to adequately excise the affected lung parenchyma. (9)

In summation, pulmonary sequestration is one of the more common congenital lung diseases. The diagnosis should be considered in any patient who presents either with an indolent basilar lobe process or a lower lobe cystic appearing lesion.

PULMONARY VASCULAR MALFORMATIONS

Pulmonary Arteriovenous Malformations

Pulmonary arteriovenous malformations (PAVMs) are functional connections between a pulmonary artery and a pulmonary vein. The first PAVM was described in 1897 by Churton. His diagnosis was made postmortem. The first antemortem diagnosis was made by Smith and Horton in 1939. In 1942 Hepburn and Dauphinee performed the first surgical excision of a PAVM. (13) Since its initial description approximately 450 cases of PAVMs have been reported. Acquired causes of PAVMs include cirrhosis, trauma, surgery, schistosomiasis and actinomycosis (14), but the majority of PAVMs are felt to be of congenital origin. Forty to sixty percent of patients with PAVM also have Osler-Weber-Rendu disease (OWRD), an autosomal dominant condition with high penetrance. It is characterized by a widespread abnormality of the vasculature with a resultant bleeding diathesis. Characteristically, the vessel walls are thin, often with only a single layer of endothelium which is lacking in support and normal contractility. Multiple organ systems are typically involved including the skin, the nasopharynx, the GI tract, and the CNS; 15% of patients manifest PAVMs. The finding of a PAVM should prompt a thorough family history and review of systems to rule out OWRD.

The etiological mechanism of pulmonary fistula formation has not been well delineated, however two theories have been postulated. First, it has been hypothesized that the defect arises at the lung bud stage of embryological development at which time a septum normally forms a primitive connection between arterial and venous plexi. During the second month of development incomplete degeneration of the vascular septum occurs and results in an AV fistula. The second hypothesis, less well defined, is that the lesion is due to a defect of the terminal capillary loops which predisposes to areas of microvascular dilation and formation of thin walled vascular sacs supplied by a distended afferent artery and drained by a distended efferent vein. (15)

Clinically, the majority of patients with PAVMs present with an incidentally discovered abnormality on chest x-ray and are asymptomatic. PAVMs are found more often in females than males and typically become manifest in the third or fourth decade. In contrast, extrathoracic AVMs present at an earlier age. (15) The classic triad of dyspnea, cyanosis and clubbing is seldom noted at the time of presentation. Dines et al at the Mayo Clinic reviewed 63 patients who had presented to their institution with PAVM over a twenty year period and noted only 28 of 63 patients (44%) had symptoms attributable to the PAVM at initial presentation. The most common presenting symptoms were dyspnea (32%) and palpitations (13%). Other authors have reported CNS manifestations such as headache, dizziness, tinnitus, transient hemiplegia and seizures as the predominant complaints at the time of initial presentation, with up to 30% of patients presenting with these symptoms. (13) In the Mayo Clinic series, a characteristic extracardiac murmur or bruit was heard in 60%. In patients in whom PAVMs were associated with OWRD, 70% had a bruit, whereas only 35% of those without OWRD had a bruit. (12) The murmur is characterized as being holosystolic, increased with inspiration, decreased with Valsalva maneuver (decreased pulmonary blood flow) and increased with a Müller maneuver (forced inspiration against a closed glottis after full expiration). Laboratory studies are remarkable for polycythemia and resting hypoxemia, although one may see anemia in patients with OWRD. Swan-Ganz monitoring usually demonstrates normal hemodynamic parameters. Chest radiographs reveal peripheral, circumscribed, non-calcified lesion(s) connected to the hilum by dilated vessels. The PAVM are characteristically closely related to the visceral pleura. (12) PAVM are predominantly found in the lower lobes (~ 60%) followed by the middle and upper lobes. Thirty to fifty percent of patients may have multiple lesions. Eight to twenty percent of patients have bilateral PAVMs. (13) The presence or absence of symptoms correlates well with the radiographic size of a single fistula as fistulas with a diameter less than 2.0 cm usually are not symptomatic. (12) Higgings and Wexler noted congenital PAVMs have four basic radiographic patterns: 1) solitary fistula, 2) multiple fistulae of varying size, 3) multiple fistulae of uniform size, and 4) diffuse fistulae (telangiectasias). Complications associated with PAVMS range from non-life threatening hemoptysis (10%) to cerebral abscess. The rupture of pleural based PAVMs is associated with hemothorax. 5-10% of patients (untreated) experience a CVA, most often a thrombotic event (increased incidence in presence of polycythemia) and occasionally a paradoxical embolic event. Rarely thrombotic masses or bacterial endarteritis may develop within the fistula with resultant metastatic cerebral and peripheral abscesses. Dependent upon the degree of right-to-left shunting (up to 78% shunt has been reported) patients suffer from hypoxemia and polycythemia. Pregnancy is thought to trigger the advancement of PAVMs secondary to increased blood flow and "hormonal growth factors" which may stimulate fistula expansion. Patients with OWRD definitely have an increased incidence of multiple fistulas, increased rate of fistula growth and an increased incidence of associated complications (20-30%) (8)

The evaluation of patients presenting with a suspected diagnosis of PAVMs should include a history, physical exam, complete blood count, and arterial blood gases. The history should include information about family members with similar disorders (OWRD) and history of bleeding difficulties. The physicalexam should focus on the examination of the skin and mucous membranes for evidence of telangiectasias and careful auscultation for extracardiac bruits. Suspected PAVMs may be radiographically evaluated by several different techniques including plain film radiographs (inspiration and expiration views to observe for size changes), tomography, fluoroscpy, CT scanning, lung perfusion scanning, contrast echo, and ultimately angiography. In the clinical situation where observation rather than therapeutic intervention is planned. non-invasive techniques are adequate to establish the diagnosis. Tomography is usually sufficient to establish the presence of an afferent "feeding" artery and efferent draining vein originating from the hilum. Fluoroscopy may be used to demonstrate a change in size of the vascular lesion with Valsalva and Muller maneuvers (15). CT scanning, especially dynamic CT scanning, can be used to delineate the origin of the vascular supply to a suspected PAVM. This is useful to determine if a PAVM derives its blood supply from a systemic source (4%) or the pulmonary circulation. (13) Using the dynamic CT scanning techniques with contrast, a time-density (opacification) relationship is observed. If the vascular anomaly opacifies in phase with the pulmonary artery or vein it is supplied by the pulmonary circulation; if opacification coincides with peak aortic opacification it is supplied by the systemic circulation. (16) Lung perfusion scanning with Tc99 microspheres of albumin is also useful in establishing the existence of a right-to-left shunt. Normally the albumin microspheres are trapped in the pulmonary capillary bed, however in the presence of a shunt the microspheres may pass into the systemic circulation resulting in uptake in the kidney and brain. The lung scan may have a "cold" area in the region of the PAVM. (15) Contrast echocardiography using either indocyanine green or normal saline bubble studies works according to the same principle, i.e. the pulmonary capillary bed filters out the bubbles and detection of bubbles in the systemic circulation indicates a shunt. This technique though sensitive is nonspecific. (17) Lastly, prior to any therapeutic intervention angiography is indicated to define the architecture and rule out other co-existent PAVMs. White et al evaluated 17 patients with a total of 91 PAVMs with the use of superselective angiography and classified the PAVMs as simple (capillary) or complex (cavernous) depending upon their architecture. In their review, 79% of the PAVMS were referred to as simple, being malformations characterized by a single feeding artery draining into a bulbous, nonseptated aneurysmal communication with a single draining vein. The remaining 21% were referred to as complex, consisting of two or more pulmonary branches communicating with a septated aneurysmal structure with two or more draining veins. (18)

Accepted indications for therapeutic intervention in patients with PAVMs include: 1) a PAVM associated shunt large enough to cause symptoms, 2) a complication of the fistula, 3) evidence of progressive PAVM enlargement, and 4) a PAVM fed by a systemic artery. Choices of therapy include surgical excision and embolotherapy. From 1942 until 1978 surgery was the only accepted form of therapy. In cases of a single PAVM limited resection of the lesion is usually accomplished without extensive resection of the pulmonary parenchyma. In cases where multiple PAVMs exist, consideration is made for a sternotomy approach when feasible (LLL lesions are not accessible) or staged posterolateral thoracotomies. The associated mortality with surgical intervention is 4-5% . (19) In 1978 Taylor et al reported the first successful mechanical interruption of afferent arteries supplying a PAVM. This was accomplished by placing steel coils with "wool tails" proximal to the PAVM. (18) Since that time, embolotherapy has become a viable treatment option. In a previously mentioned study, White et al reported their experience with embolotherapy, with a technique using a detachable silicone filled miniballoon. They embolized PAVMs with a diameter between 3 and 9mm. In 16 patients, 68 PAVMs were embolized using this technique. Fourteen of sixteen patients experienced an increase in PaO2 and oxygen saturation. Follow-up angiograms in 5 of 14 patients, performed 3 days to 4 years after the procedure, documented permanent PAVM obliteration. Complications occurred in 2 of 16 patients and included small pulmonary infarctions related to proximal placement of the occluding balloon or possible hypercoagulable state secondary to polycythemia. One patient experienced a paradoxical "balloon" embolus to the liver. (18) White feels miniballoon embolotherapy is superior to the use of standard embolic materials as the potential for paradoxical embolism is reduced. He also notes they did not perform embolotherapy on large PAVMs because of this risk. In summation, there are no clinical trials to compare treatment versus non-treatment of PAVMs, however as noted the natural history of PAVMs is far from benign and the complications of therapy appear much lower than the risks of non-treatment. (20,21,22).

Scimitar Syndrome

The scimitar syndrome is an interesting but rare anomaly with a constellation of several cardiopulmonary defects. The typical syndrome demonstrates the following defects: 1) hypoplasia of the right lung with dextroposition of the heart, 2) hypoplasia of the right pulmonary artery, 3) anomalous arterial supply to the right lower lobe from the abdominal aorta, and 4) anomalous venous drainage of the right lung into the inferior vena cava. (23) The partial or total anomalous venous drainage of the right lung into the inferior vena cava or the azygos system is present in all cases. The anomalous vessel characteristically presents as a broad curvilinear shadow on chest x-ray coursing from the hilum towards the diaphragm, and was initially felt to resemble a Turkish sword or "scimitar."

The majority (>95%) of cases involve the right lung and there is a slight female predominance with a female:male ratio of 1.4 to 1.0. Though the previously listed findings are "classic", the syndrome may present in various ways. Approximately 25% of patients have associated congenital heart disease. The most common defect is an atrial septal defect. Other associated anomalies include tetralogy of Fallot, PDA, coarctation of the aorta and a VSD. Diaphragmatic abnormalities have been reported in 21%. (30) The syndrome usually presents as an unusual finding on routine chest x-rays or in symptomatic patients with complaints of dyspnea or recurrent infection. The scimitar vein usually drains the whole lung, however in some cases the upper lobe may drain normally into the left atrium. In the majority of cases the right lung receives an aberrant arterial blood supply from branches of the abdominal aorta. The venous drainage into the vena cava constitutes a left-to-right shunt. (28)

A variety of studies may be used to document the presence of scimitar syndrome. Plain radiographs normally demonstrate the scimitar vein, however it may be obscured behind the heart. Bronchography often demonstrates right bronchial hypoplasia, and errors of segmentation and lobation are frequent. Angiography, digital subtraction angiography and dynamic CT scanning can confirm the arterial supply and venous drainage associated with the syndrome. (25)

Therapy is reserved for patients with severe symptoms. Recurrent infection may necessitate a pneumonectomy. A symptomatic left-to-right shunt may be corrected by rerouting the blood flow from the scimitar vein back into the left atrium.

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PATHOGENESIS AND TREATMENT OF COPD

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INTRODUCTION

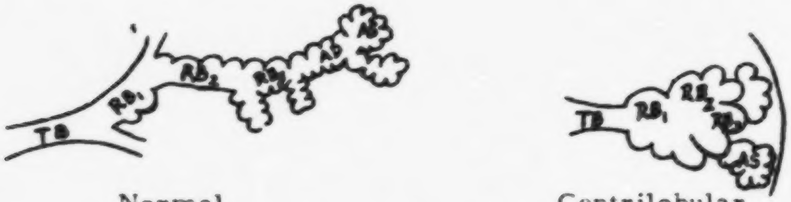
Chronic obstructive lung disease is actually a syndrome encompassing several diseases including chronic bronchitis, emphysema, and asthma. Although the majority of patients with COPD have both chronic bronchitis and emphysema, these two diseases have distinct pathophysiologies as well as different modes of therapy.

PATHOGENESIS OF COPD

Emphysema

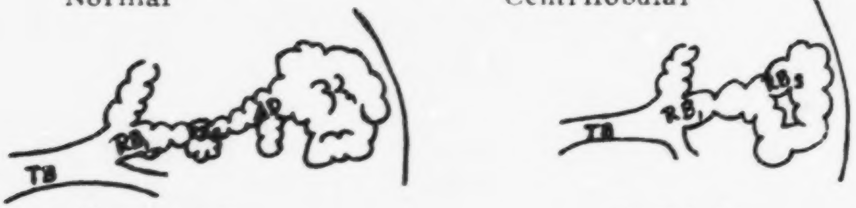
Pulmonary emphysema is an anatomical diagnosis, defined as enlargement in the respiratory portion of the lung beyond the terminal bronchiole (the acinus) accompanied by destructive changes (1). Emphysema has been further classified according to that portion of the acinus involved: (a) the respiratory bronchiole (centrilobular or centriacinar emphysema), (b) the distal acinus, consisting of alveolar ducts and sacs (paraseptal or periacinar emphysema), or (c) the entire acinus (panlobular or panacinar emphysema) (Figure 1).

Figure 1



Normal

Centrilobular



Paraseptal

Panlobular

TB - terminal bronchiole
AD - alveolar duct
RB - respiratory bronchiole
AS - alveolar sac

It is postulated that these different types of emphysema are produced by an imbalance between lung proteases and antiproteases. The mechanism of centrilobular emphysema, which is usually secondary to cigarette smoking, is based on such an imbalance. In the smoker's lung there is an increased collection of both leukocytes and macrophages in the respiratory bronchioles. These cells seem to aggregate where the aerosolized smoke particles tend to fall in the respiratory bronchiole. Both the leukocyte and macrophage release elastases which in experimental animals will cause emphysema if not neutralized by antiproteases. In human lungs approximately 90% of the antiprotease activity is due to alpha-1 antitrypsin, with a smaller part due to an alpha-2-globulin. Oxidizing chemicals in cigarette smoke will inactivate alpha-1 antitrypsin in vitro. Thus, the cigarette smoke causes more elastases to accumulate in the lung, while depressing local anti-elastase activity. The net result is damage to lung parenchyma and bronchioles. Although injury occurs throughout the lungs, destructive changes are most severe in the apices because they are subject to the highest mechanical stresses, thus resulting in the predominantly apical distribution seen in smoker's centrilobular emphysema (4).

Panlobular emphysema, which is seen in alpha-1 antitrypsin deficiency, occurs predominantly in the bases of the lung. Because blood flow is greatest in the bases, more leukocytes are sequestered in those regions. These leukocytes release proteases and elastases when they die. If no alpha-1 antitrypsin is available to neutralize these enzymes, then lung destruction may occur. Because the leukocytes are present throughout the entire acinus, all of the acinus is exposed to the digestive enzymes and panlobular emphysema occurs (Table 1).

Table 1

COMPARISONS OF ALPHA 1 AND COMMON EMPHYSEMA

Type of Emphysema	Pathology	Elastase	Inhibition	Site in Lung
Alpha-1 deficient	Pan lobular	Neutrophil	Alpha-1 antitrypsin	Base
Common	Centrilobular	Alveolar Macrophage Neutrophil	Alpha-1 and Alpha-2 Globulin	Apex

Distal emphysema or "paraseptal emphysema" involves the distal or peripheral portion of the acinus. It is thought to be the type of emphysema associated with spontaneous pneumothorax in young adults (1), but is otherwise not particularly significant. Etiology is unknown.

The destruction of alveolar walls, with the resulting loss of internal surface area and of elastic recoil, is reflected in pulmonary function testing. The functional residual capacity (FRC) is normally determined by the balance point between the chest wall pulling outward and the elastic recoil of lungs collapsing inward. Thus emphysema, through loss of elastic recoil, produces loss of inward force and the FRC will increase. Loss of lung recoil allows airways to collapse at high lung volumes during forced expiratory maneuvers (air trapping) and the residual volume (RV) increases. Total lung capacity is also increased in emphysema (5). Less pressure is required to inflate the lung, thus static compliance is increased. Loss of internal surface area and reduction of vascular supply to the emphysematous areas results in a reduction of the DLCO and DL/VA (6). In most emphysema patients, the simultaneous destruction of ventilating units together with their blood supply maintains a relatively normal ventilation (V) to perfusion (Q) ratio, resulting in only mild hypoxemia (5).

Chest x-ray findings consistent with emphysema include diaphragmatic flattening, increase in depth of the retrosternal air space, attenuation of pulmonary vasculature of the outer half of the lungs, and irregular radiolucency of lung fields (7).

Chronic Bronchitis

Chronic bronchitis, a clinical diagnosis, is defined as chronic excessive mucus production in the airways which is not due to specific diseases such as bronchiectasis, tuberculosis, asthma, etc. Chronic is defined as three months per year for two or more successive years. Anatomically, patients with chronic bronchitis are found to have both an increase in number and size of the tracheobronchial mucous glands. The Reid index, a histologic measurement of bronchial wall thickness (inner perichrondrium to basement membrane), is increased in chronic bronchitis, and has been said to correlate with disease severity (1). However, although it appears that the bronchial musculature is increased in size, no positive correlation can be made with the clinical aspect of chronic bronchitis. Other inflammatory changes, i.e. edema and globlet cell hypertrophy, do not correlate with the clinical course of chronic bronchitis and cannot be used as diagnostic criteria. The increased size and numbers of mucous glands along with the heavy mucous secretions block the lumina of the airways and lead to airway obstruction and distal infection.

Although there are frequently no distinctive radiologic features, findings may include an increase in lung markings ("dirty chest"), bronchial wall thickening, or bronchographic abnormalities (8).

Pulmonary function testing reveals obstructive defects produced from the narrowing or frank blockage of airways. Air trapping due to mucus occluding small airways may increase the RV. FRC may be normal, or, if expiration is markedly prolonged preventing emptying of the airways before the next inspiration, may be increased. As opposed to emphysema static compliance is normal because the lung parenchyma is not destroyed. The best simple test to separate emphysema from chronic bronchitis is the DLCO, since in chronic bronchitis the DLCO should be normal (9) or only mildly decreased, due to the relative preservation of lung tissue and vascular supply.

OUTPATIENT MANAGEMENT OF COPD

The management of the patient suffering from chronic obstructive pulmonary disease (COPD) should be directed at reducing the work of breathing, achieving maximal lung function, alleviating hypoxemia, preventing acute exacerbations and increasing the efficiency of energy utilization and performance of daily activities (10). The impact of treatment on survival has been difficult to quantitate, with two major exceptions.

It is clear that early diagnosis with risk factor modification, i.e. cessation of smoking, is the most important clinical intervention in modifying the course of the disease. Prognosis correlates directly with FEV_1/age. It has been demonstrated that heavy smokers (>15 cigarettes per day) with COPD have a decline in FEV_1 of 75-80ml per year (11), as opposed to nonsmokers who average 30ml per year decrease in FEV_1 due to aging (12). A recent study by Camilli et al has shown that quitting smoking has a beneficial effect on the rate of decline in FEV_1 (13). The greatest benefit was seen in persons less than age 35, with improvement in FEV_1 occurring in both men and women. In the 35-50 age group, the decline in FEV_1 was similar for those who quit and those who had never smoked. In patients between age 50 and 70, FEV_1 decline was intermediate between those who continued to smoke and those who never had.

The other area where therapy has clearly altered survival is the treatment of hypoxemia. The British Medical Research Council trial showed that hypoxic patients with cor pulmonale had improved survival when given oxygen for 15 hours out of 24, including nighttime (14). The National Heart, Lung and Blood Institute (NHLBI) trial compared nocturnal oxygen therapy (12 hours a day) with "continuous" oxygen therapy (at least 18 hours a day) (15). In the NHLBI trial, patients were entered into the study if (1) their P_aO_2 was 55 torr or less whatever their associated symptoms, or (2) if their P_aO_2 was 56-59 torr and (a) there was clinical or electrocardiographic evidence of cor pulmonale, or (b) their hematocrit was 55% or greater. Both studies required the patients to be stable on maximal conventional therapy prior to entry.

Other therapeutic maneuvers commonly employed by the pulmonologist have failed to clearly demonstrate a positive impact on survival when independently analyzed. However, systematic respiratory care appears to provide improvement in exercise tolerance, reduce hospitalization, reduce symptoms, and lead to significant reduction in anxiety, depression and somatic concerns, thus generally improving quality of life (10). Therefore, treatment appears to be warranted and is considered the standard of care (16). The following sections will review common strategies employed in the comprehensive care of COPD.

BRONCHODILATORS

Beta Agonists and Anticholinergics

It is often difficult to demonstrate objective improvement with bronchodilator therapy in COPD, partly because the disease process is characterized by irreversible flow obstruction. Nevertheless, some patients (~10%) with COPD have an unexpected marked improvement with bronchodilator therapy (17). Bronchodilator therapy is an essential part of a bronchial hygiene program, promoting clearance of secretions and prophylaxing against bronchospasm.

Beta agonists are preferentially administered via the inhaled route. This mode of administration offers the best benefit to toxicity ratio when compared to oral administration (18). There are a number of beta adrenergic bronchodilators to choose from (see Table 2), but the long acting beta-2 specific agents are preferred.

TABLE 2

Table 2 ***Pharmacologic Characteristics of Selected Sympathomimetic Bronchodilators****

DRUG	RECEPTOR ACTIVITY	ROUTES OF ADMINISTRATION	EFFECTIVE DOSE RANGE (mg)	DURATION OF ACTION (hours)
Epinephrine	alpha = beta$_1$ = beta$_2$	Subcutaneous	0.25 to 0.5	0.5 to 2
Isoproterenol	beta$_1$ = beta$_2$	Inhaled	0.08 to 0.16	0.5 to 2
Isoetharine	beta$_1$ < beta$_2$	Inhaled	0.5 to 1.0	1 to 4
Metaproterenol	beta$_1$ < beta$_2$	Inhaled	0.65 to 1.3	3 to 4
		Oral	10 to 20	6 to 8
Terbutaline	beta$_1$ < beta$_2$	Inhaled	0.2 to 0.4	3 to 4
		Subcutaneous	0.25 to 0.5	1 to 4
		Oral	2.5 to 5	6 to 8
Albuterol	beta$_1$ << beta$_2$	Inhaled	0.1 to 0.24	4 to 6
		Oral	2 to 4	6 to 8
Bitolterol	beta$_1$ << beta$_2$	Inhaled	0.37 to 0.74	5 to 8

*Adapted from Mahler, D. A. Pulmonary aspects of aging: Chronic obstructive pulmonary disease. *In* Gambert, S. R. (ed.) Contemporary Geriatric Medicine, Volume 1. New York, Plenum Publishing Company, 1983

Metaproterenol, terbutaline and albuterol tend to be the most popular agents in the United States.

Recent work by Gross and Skorodin has shown that anticholinergic agents (atropine methonitrate) may provide more bronchodilatation than beta adrenergic agents (19,20). Widespread use has been limited by lack of standardization of dosing and by side effects, which may include tachycardia, xerostomia, urinary retention, ileus, mental status changes and exacerbation of glaucoma. Ipratropium bromide (Atrovent), a quaternary ammonium compound does not cross the blood-brain barrier and therefore produces many fewer side effects. Ipratropium is currently available in a metered dose inhaler in the United States. The exact role of anticholinergic agents in the treatment of COPD remains to be defined. They appear to offer an alternative to maximal doses of beta agonists (21). The role of anticholinergics in combination with beta agonists is less well defined, although combination therapy may be of benefit in special circumstances (22).

Metered dose inhalers (MDI) offer a convenient and effective method of drug delivery providing they are used optimally. Major errors in technique may occur, particularly in elderly patients who experience difficulty in coordinating activation of the MDI with the respiratory maneuver. To insure adequate drug delivery, the patient must be properly instructed (see Table 3) and repeatedly observed in the outpatient clinic.

Table 3

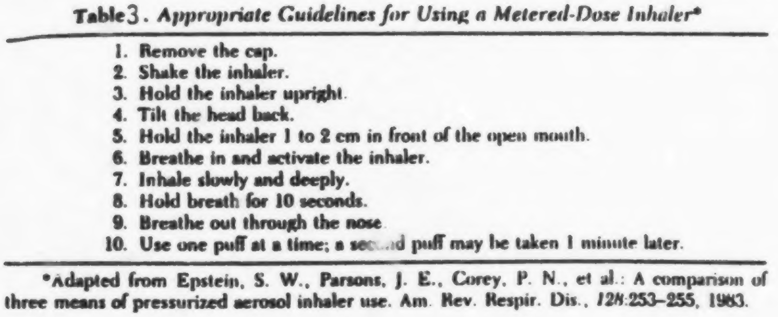


Table 3. *Appropriate Guidelines for Using a Metered-Dose Inhaler**

1. Remove the cap.
2. Shake the inhaler.
3. Hold the inhaler upright.
4. Tilt the head back.
5. Hold the inhaler 1 to 2 cm in front of the open mouth.
6. Breathe in and activate the inhaler.
7. Inhale slowly and deeply.
8. Hold breath for 10 seconds.
9. Breathe out through the nose.
10. Use one puff at a time; a second puff may be taken 1 minute later.

*Adapted from Epstein, S. W., Parsons, J. E., Corey, P. N., et al.: A comparison of three means of pressurized aerosol inhaler use. Am. Rev. Respir. Dis., *128*:253–255, 1983.

In patients who fail to use the MDI effectively the addition of a spacer (see Figure 2) or large volume reservoir may be advantageous.

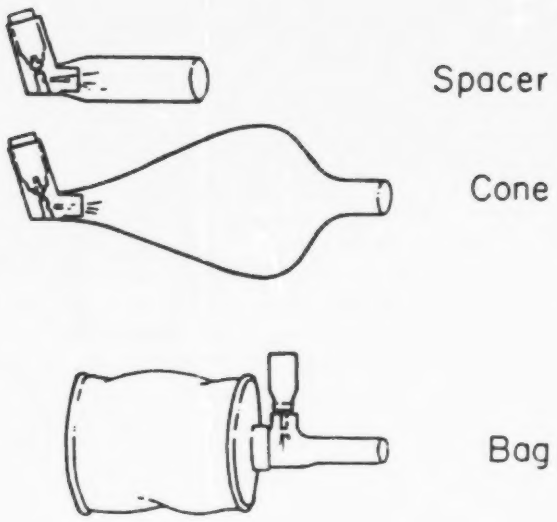


Figure 2 Three devices designed to increase the efficiency of aerosol deposition in the lung while decreasing large droplet deposition in the mouth and pharynx.

There are a small group of patients with COPD who cannot master the MDI with the spacer despite repeated instruction. This may be due to lack of strength (inability to discharge the inhaler or collapse the bag) or lack of coordination. These patients do best with home nebulizer units.

Drug administration with intermittent positive pressure breathing (IPPB) confers no therapeutic advantage over compressor nebulizer (CN) therapy (24). In addition, IPPB therapy is more expensive than CN therapy and may result in inadvertent barotrauma.

Theophylline

The use of theophylline preparations in patients with COPD remains controversial, in part because therapy can be complicated by unwanted side effects and the low therapeutic to toxic ratio. These agents are generally employed in patients with moderate to severe flow obstruction. Although they are classified as bronchodilators, they are mild bronchodilators at best, and therefore second line agents in treating bronchospasm.

The rationale for theophylline use in COPD is based on the nonbronchodilator as well as bronchodilator effects (24). Theophylline may improve cardiac performance via its diuretic, chronotropic, and inotropic effects. Work by Ambier suggests that theophylline increases respiratory muscle strength and delays the onset of diaphragmatic fatigue in patients with COPD. Sustained-release theophylline has been shown to reduce the sensation of breathlessness in patients with "nonreversible" obstructive airway disease (25). Theophylline may stimulate hypoxic ventilatory drive(26).

The exact mechanism by which it works is unknown. The traditional concept that theophylline relaxes smooth muscle by increasing 3'5' cyclic adenosine monophosphate (cAMP) via inhibition of phosphodiesterase has been questioned. Theophylline has only been shown to be a phosphodiesterase inhibitor in "in vitro" studies using toxic concentrations of the drug (27). Alternative mechanisms that have been proposed include antagonism of prostaglandins, effects on intracellular calcium, increased binding of cAMP to its binding protein and increased contractility of the diaphragm (28).

There appears to be little or no benefit to maintaining high therapeutic (15-20ug/ml), as opposed to low therapeutic (10-15ug/ml), levels in patients with COPD. The dose response curve for theophylline is not linear, the incremental improvement in FEV_1 seeming to lessen above a serum level of 10 - 12 ug/ml (28,29). This is consistent with the study by Eaton that failed to demonstrate any significant difference in efficacy between low dose theophylline (mean serum level, 10.9 ug/ml) and high-dose theophylline (mean serum level, 18.9 ug/ml) in COPD (30).

About 90% of theophylline is metabolized in the liver by the microsomal oxidative enzymes employing the cytochrome P-450 system. A number of host factors and drug interactions may interfere with theophylline metabolism (see Table 4).

Table 4

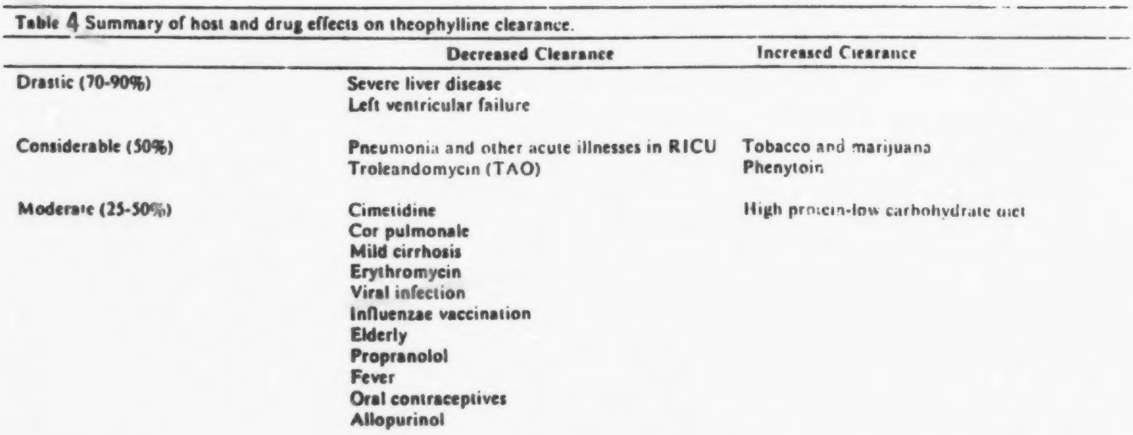


Table 4 Summary of host and drug effects on theophylline clearance.

	Decreased Clearance	Increased Clearance
Drastic (70-90%)	Severe liver disease Left ventricular failure	
Considerable (50%)	Pneumonia and other acute illnesses in RICU Troleandomycin (TAO)	Tobacco and marijuana Phenytoin
Moderate (25-50%)	Cimetidine Cor pulmonale Mild cirrhosis Erythromycin Viral infection Influenzae vaccination Elderly Propranolol Fever Oral contraceptives Allopurinol	High protein-low carbohydrate diet

If the decision is made to treat a patient with COPD with a theophylline preparation, slow release preparations at 8 or 12 hour intervals are preferred because of convenience and steady drug levels. The 24 hour preparations should be avoided particularly in elderly patients because of large peak to trough differences and the possibility of "dose-dumping" if taken with food. A reasonable approach to initiating theophylline therapy is outlined in Table 5.

Table 5

ORAL DOSING RECOMMENDATIONS

1. Begin the dose at 300-400 mgs/24 hours for one week

   This is referred to as the "adaptation phase". Patients who may have transient caffeine-like side effects such as nausea, stomach queasiness or nervousness will adapt to theophylline better if the dose is reduced at first.

2. Increase to full doses if the patient tolerates the reduced dose

   These doses tend to be 500-600 mg/24 hours in nonsmokers and 800-900 mg/24 hours in smokers. Patients with cor pulmonale, left heart failure, liver disease, the elderly, and those who are small in stature may need to have a smaller initial dose.

3. Measure serum theophylline after 48-72 hours of no missed doses.

4. Make the final adjustment

   Increases should be kept to 28% at a time because levels may rise out of proportion to the dose increase. The availability of new office fingerprick techniques for theophylline measurement will facilitate this.

(Adapted from Jenne JW, Drug Therapy of Asthma Part 1: Beta-Adrenergic Agonists and Theophylline Pulmonary Clinical Update (Dec 1985)

Steroids

While reasonable data exists to support the use of steroids in exacerbations of COPD, the utility of corticosteroids in stable COPD is controversial (31,32). Short term treatment (less than 4 weeks) is generally not associated with significant toxicity. However, long term daily corticosteroid use may result in a number of significant complications including adrenal suppression, cushingoid appearance, cataracts, osteoporosis, aseptic necrosis, increased susceptibility to infections, glucose intolerance, myopathy and hypertension.

The proposed benefits of corticosteroids involve suppression of airway inflammation, inhibition of prostaglandin synthesis or release, and potentiation of catecholamine stimulation of cyclic AMP synthesis. The question remains, what patients, if any, should be treated with steroids and how can these patients be identified?

A trial of corticosteroids appears to be reasonable in patients who show a partial response to theophylline or beta agonists; patients who have severe COPD with an FEV_1 of less than 1 liter; and patients who are limited significantly by their lung disease (35,36,37). A small percentage (15-30%) of patients will respond (33). Response should be documented by an objective improvement in spirometry.

A reasonable trial consists of 40-60 mg of prednisone or its equivalent daily for two to three weeks. If the patient fails to improve with the corticosteroids, therapy should be promptly discontinued. If there is a response, the drug should be tapered to its lowest possible dose, preferably on an alternate day regimen. Many patients cannot be lowered below 10-15 mg/day of prednisone. Only very select patients can be stabilized on inhaled beclomethasone four puffs four times a day (36), but inhaled steroids may allow a reduction in oral steroid dosage even when the patient cannot tolerate total withdrawal.

Antibiotics

A recent study by Anthorisen et al has demonstrated that broad spectrum antibiotics are of benefit in exacerbations of COPD (37). Particularly in exacerbations that involved dyspnea, increased sputum volume, and sputum purulence (type I exacerbations), antibiotic usage resulted in a 20% decrease in mucus rate compared to placebo, while there was a 30% deterioration in placebo versus treated group. The antibiotics used were amoxicillin, doxycycline, and trimethoprim sulfamethoxazole in 10 day courses. These antibiotics cover the most common bacterial pathogens associated with decompensation - *Streptococcus pneumoniae* and *Hemophilus influenzae*.

Despite the fact that the majority of infectious exacerbations in COPD may be related to viruses, the above study supports prompt treatment of exacerbations with antibiotics, particularly when dyspnea, increased sputum volume and sputum purulence are present. A 10 day course of ampicillin-amoxicillin. tetracycline/doxycycline, cephalosporin or trimethoprim-sulfamethoxazole appears reasonable. If the patient fails to improve on any of the first three agents, tracheobronchitis secondary to nontypable H. influenzae or Branhamella catarrhalis should be considered. These organisms are more commonly associated with lower respiratory tract pathology than previously believed (38,39). Both trimethoprim-sulfamethoxazole and amoxicillin-clavulanic acid have good activity against these organisms.

Oxygen

As mentioned previously, oxygen has been shown to improve survival in select patients with COPD. Patient criteria for oxygen therapy are listed in table 6. A portable liquid oxygen system is preferable in ambulatory patients. An oxygen reservoir (mustache or pendant) can decrease the monthly cost of oxygen therapy to the patient. Patients with refractory hypoxemia on a conventional O_2 system may benefit from transtracheal oxygen therapy (40).

Table 6

Table 6 *Indications for Chronic Home Oxygen Therapy in Patients with Chronic Obstructive Lung Disease*

$PaO_2 \leq 55$ mm Hg on two occasions 3 weeks apart when the patient is stable on optimal therapy

$PaO_2 \leq 59$ mm Hg with associated
- edema
- hematocrit ≥ 55%
- p pulmonale on ECG 3 mm in leads II, III, aVf
- mental dysfunction

Selected patients with PaO_2 during exercise ≤ 55 mm Hg and exercise intolerance (see text)

Selected patients with $PaO_2 \leq 55$ mm Hg during sleep with documented and unexplained
- pulmonary hypertension
- cor pulmonale
- erythrocytosis
- mental dysfunction

ADJUNCTIVE THERAPY

Mucolytics and Expectorants

There appears to be no additional benefit to adding mucolytics (N-acetylcysteine) or expectorants (guaifenesin, terpin hydrate, ammonia, potassium iodide, or ipecac) to a regimen of inhaled bronchodilators (41). N-acetylcysteine can worsen bronchospasm. Oral hydration has been shown to have no effect on the characteristics of sputum in patients with chronic bronchitis (42).

Pneumococcal Vaccine/Influenza Prophylaxis

All patients with COPD should be offered the pneumococcal vaccine. A single dose of the vaccine is judged to be sufficient. A yearly flu vaccine should be offered as well. The protection rate is felt to be 60-80%. In documented outbreaks of influenza A, prophylaxis with amantidine is indicated, especially when the patient has not been vaccinated or has received it only recently.

Rehabilitation

Studies have shown that pulmonary rehabilitation has improved quality of life and decreased the need for hospitalization. Programs can be cost effective. Patient education may be furthered by the attendance of "Better Breathing Clubs" which are sponsored in many communities by the American Lung Association.

Percussion and Postural Drainage

These maneuvers appear to be effective in chronic bronchitic patients who produce >30cc sputum/day (43).

Miscellaneous

An anginal equivalent presenting as dyspnea, gastroesophageal reflux (related to therapy, or spontaneous disease), or sinusitis (frequently occult) may complicate the care of COPD patients in the outpatient setting. A high degree of suspicion is necessary to appropriately diagnose these problems.

MANAGEMENT OF RESPIRATORY FAILURE IN COPD

Introduction

Respiratory failure in COPD represents one of the most challenging problems in pulmonary medicine. Unlike asthmatics these patients may have no reversible component to their airway obstruction. The mortality and morbidity is, therefore, greatly increased.

Definition

Whenever acute respiratory failure develops in COPD, an underlying reversible factor should be sought. Common causes are acute bronchitis, congestive heart failure, sedation, uncontrolled oxygen administration, pulmonary emboli, pneumothorax, and pneumonia. However, many patients will seem to have developed "idiopathic decompensation".

Treatment

The general philosophy is to treat all patients as though they have reversible airway obstruction, while searching for other reversible etiologies for the patient's decompensation.

1. Aminophylline (44,45) - Intravenous dosage rates used in the past resulted in toxic blood levels in many patients. Due to tremendous differences in metabolism of the drug (half-life varies from 4.5 to 13 hours), all formulas are only guidelines and blood levels are mandatory. All dosages are calculated from lean body weight. In adults not currently receiving theophylline products, a loading dose of 6 mg/kg followed by a continuous infusion of 0.5 to 0.6 mg/kg is recommended by the FDA. This loading dose will raise the serum level approximately 10 ug/ml. For patients who have been taking regular theophylline, a loading dose should not be used, or should at least be drastically reduced until a baseline serum theophylline level is known. In patients with liver dysfunction or congestive heart failure, the loading dose is the same, but the maintenance dosage is reduced to 0.2-0.3 mg/kg per hour; serum levels are critical in making further adjustments.

2. Steroids (46-47) - It is impossible to predict which patient will respond to short term high dose steroids. Optimal dosage is not known, but 0.5 mg/kg Solumedrol (or equivalent) intravenously every 6 hours for 72 hours has been effective in a double blind trial.

3. Sympathomimetics (48,49) - Nebulized metaproterenol and albuterol are relatively effective beta-2 selective bronchodilators. The current recommended dose for nebulized metaproterenol is 0.3cc in 1.5cc normal saline every 4-6 hours. Recommended dose for nebulized albuterol is 0.5cc in 2.5cc normal saline every 4-6 hours. Cardiovascular side effects are minimal but the development of tremor and nervousness may limit patient acceptance and compliance.

4. Oxygen (50) - Low flow oxygen is the cornerstone of management. It must be applied quantitatively with a goal of a PaO_2 of 60mm Hg. In the unstable patient a 24-48% Venturi mask is best for initial treatment since the FiO_2 delivered is accurate despite large changes in minute ventilation because of the high flow (40-100 L/min) of gas (oxygen plus entrained air) through the mask. If the patient is more stable, nasal prongs at 1-2 L/min are more acceptable since they allow for eating, drinking, etc. However the FiO_2 delivered to the patient in this low flow delivery system is dependent on total minute ventilation and respiratory pattern.

Low-flow oxygen should not be abandoned due to mild CO_2 retention, as long as the pH remains >7.2. Most patients will respond to this conservative management and will not require intubation. If marked respiratory acidosis does occur, the patient must never be withdrawn from oxygen in order to stimulate hypoxic drive, since this almost always results in critical hypoxemia. The next step, if further efforts are to be pursued, is intubation with mechanical ventilation.

INTUBATION

The decision to intubate is never easy. Quality of life, precipitating factors, underlying illnesses, and the wishes of patient and family all help in one's assessment. Most patients respond to conservative management as outlined previously. Indications for intubation are (1) semi-coma or coma, and (2) progressive respiratory acidosis (pH <7.2) despite maximum conservative therapy. Note that $PaCO_2$ and tests of pulmonary function are not included as indications for intubation.

The complications of mechanical ventilation in COPD are numerous (51). Gram negative pneumonia, atelectasis, pneumothorax, GI bleeding, metabolic alkalosis, and cardiac dysrhythmias are only a few. The longer the mechanical assistance the greater the chance of complications. Thus, weaning should be begun almost immediately. In general, weaning can begin when the patient has a FVC >1000cc, tidal volume >300cc, and an inspiratory pressure of greater than -25cm H_2O. He must also be oxygenating satisfactorily with a FiO_2 <50% because it is difficult to deliver a higher FiO_2 without a ventilator.

IMV (intermittent mandatory ventilation) is probably the most popular method of weaning (52,53); it is beyond the scope of this chapter to discuss the pros and cons of the different methods of weaning. In IMV, a bag with a one-way valve allows the patient to take spontaneous breaths between mechanical ventilations. The rate of the ventilator is slowly reduced until the machine rate is 2-4 breaths/minute. At this point, he is allowed to breathe on his own from a T-piece, receiving oxygen and humidification. The patient is allowed longer and longer periods off the ventilator until he is finally extubated. IMV allows the patient to set his own breathing pattern and may preserve muscular strength.

Not all physicians use IMV, or measure pulmonary function. Some patients never fulfill the criteria above for extubation but nevertheless do well off the ventilator. In general, if a patient fulfills the following criteria then he usually can be weaned successfully:

1. Able to handle secretions with effective cough.
2. P_aO_2 >50-60mmHg on FIO_2 <50%.
3. Alert and cooperative mentally.
4. Able to maintain adequate minute ventilation for 2-4 hours on a Briggs T-piece.

PROGNOSIS

Seventy-five percent of patients survive an episode of acute respiratory failure, but only 50% are still alive at one year, and only 30% at two years (55,56). Obese patients with chronic bronchitis do better than patients with primary emphysema.

CONCLUSIONS

Conservative management with low flow oxygen is warranted as a trial in all COPD patients with acute respiratory failure. Patients are given antibiotics, steroids, bronchodilators, hydration, and chest physiotherapy if indicated. IPPB may have a role in selected circumstances. Intubation may be indicated if patients do not respond to conservative therapy. Acute mortality is 30% and one year survival is 50%.

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ALPHA-1 ANTITRYPSIN DEFICIENCY

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INTRODUCTION

Alpha-1 antitrypsin deficiency was first described in 1963 by Laurell and Erikson in Sweden while routinely surveying serum protein electrophoretic patterns. Their patients had several characteristics that differed from their "usual" emphysematous patients. These included 1) age of onset of dyspnea relatively early (60% less than age 40), 2) no preceding history of chronic bronchitis, 3) higher female:male ratio than "usual" emphysema, and, 4) chest x-ray findings of loss of vascularity in the lower lobes bilaterally. Since this initial report, hundreds of cases have been described (1,2).

CHARACTERISTICS OF ALPHA-1 ANTITRYPSIN (AAT)

Alpha-1 antitrypsin is a glycoprotein (MW 54,000) consisting of a single polypeptide chain with 12% carbohydrate. It is found in nearly all body fluids including tears, lymph, serum, semen, breast milk, saliva, and bile. It has a serum half-life of 7 days, and is both produced and metabolized exclusively in the liver. AAT's major function is to inhibit leukocyte and macrophage elastase and collagenases. Other enzymes which are inhibited include plasmin, renin, kallikrein, and thrombin. The significance of their inhibition by AAT is unknown (37).

GENETICS AND INCIDENCE

The inheritance of AAT suggests multiple autosomal codominant alleles at one locus with each allele controlling the production of one kind of AAT molecule uninfluenced by the corresponding allele on the other member of the chromosome pair. The locus on the chromosome is designated Pi (protease inhibitor), and the individual alleles are called PiM, PiS, PiZ, etc. The position of the letter in the alphabet depends on the electrophoretic mobility with letters early in the alphabet having the fastest mobility toward the anode. There are now more than 55 Pi alleles described, but the three most common are PiM, PiS, and PiZ.

The PiM allele is the most common and is found with a prevalence of 86% to 99% in all populations. PiS occurs with a prevalence of 3%, and PiZ occurs with a prevalence of 1.6% in

Sweden. A Pi NULL/NULL pattern which represents complete absence of AAT in the serum has been reported. Common heterozygotes include PiMZ, PiMS, and PiSZ; they occur with a prevalence of 2.2-3.0%, 1.5 to 8.0% and .1% respectively (4-7).

There is no functional or immunological difference in the AAT generated by the different alleles, and no inactive form of AAT has been found. The only difference between the different phenotypes is the quantity of AAT in the serum, and the electrophoretic differences in the AAT. Of clinical importance are the alleles that lead to a lower concentration of AAT. Common phenotypes and their serum AAT concentrations are:

PiMM - normal serum level (200 mg%)
PiZZ - 15-20% normal level
PiMZ - 60% normal level
PiSS - 65% normal level
Pi NULL/NULL - 0% normal level

AAT is an acute phase reactant. The normal serum level of 200 mg% can increase 2-3 times with stress, infection, or estrogens. Severely deficient patients (PiZZ) cannot raise their serum AAT levels significantly with stress, but moderately deficient patients (PiMZ, PiMS) can elevate their serum level if stressed. This means that a normal serum level of AAT may not detect the heterozygote PiMZ under certain clinical conditions (8-11, 38).

The basic biochemical defect responsible for some of the variant AAT glycoproteins has been studied. In PiZZ the basic defect is a lysine-glutamic acid substitution in the amino acid chain. Alterations in the carbohydrate content of the variant proteins is probably due to the altered protein configuration.

DIAGNOSIS

a. Protein Electrophoresis - Alpha-1 antitrypsin comprises about 90% of the alpha-1-globulin fraction on the serum protein electrophoresis. Thus in PiZZ one may see no alpha-1 globulin on SPE. One must look at the actual tracing itself to make the diagnosis - the quantity recorded may be inaccurate!

b. Immunodiffusion assay - This test is more accurate than the SPE screening and measures the protein concentration of AAT by the antigen-antibody diffusion method. Serum levels above 40% of normal rule out serious deficiency (i.e. PiZZ). In patients with levels below that, Pi typing is recommended for more definitive identification.

c. Pi Typing - This is only required if serum level is below 40% of normal, for accurate phenotype identification. Methods are:

(1) Acid-starch gel electrophoresis - This test magnifies the mobility of proteins so that the alpha-1 globulins are separated into a series of bands of variable density.

(2) Crossed starch gel immunoelectrophoresis - The bands produced by the acid-starch gel electrophoretic method are exposed to an electrical current at right angles during exposure to an antibody directed at AAT; thus the bands are transformed into a series of peaks.

(3) Isoelectric focusing - The most definitive method for accurate Pi typing (2,12).

PATHOPHYSIOLOGY

Over the past twenty years research on AAT deficient patients has yielded significant insight into the pathophysiology of emphysema. These studies support the following hypotheses:

a. Lung injury results from an imbalance between elastase and antielastase.

b. AAT is the major antielastase of the normal human lower respiratory tract.

c. Deficiency results in no protection against neutrophil elastase in the lower respiratory tract.

d. The lack of antiprotease protection in PiZZ individuals is a chronic process.

e. Smoking produces an "acquired" alteration in elastase-antielastase balance by decreasing AAT activity as much as 20%.

f. Smoking also attracts more leukocytes within the lung resulting in greater amounts of elastase.

In summary, emphysema is felt to be the result of an imbalance between elastase and antielastase in the lung. This imbalance may be the result of AAT deficiency or smoking. Both may act synergistically to produce severe emphysema at an early age (1,13-15, 36).

CLINICAL FEATURES

PiZZ and PiZS patients have severe deficiencies in AAT and therefore have an increased incidence of panacinar emphysema and cirrhosis. Their most notable features include:

a. Symptoms of dyspnea occur below age 40 in 60% and by age 50 in 90% of smokers

b. Median age at onset of dyspnea is 40 in smokers and 53 in non-smokers (16-19).

c. Neonatal hepatitis occurs in 10-20% of all PiZZ infants; most cases resolve acutely but 25% of these patients will develop cirrhosis and chronic liver failure by adolescence (20,21).

d. Liver disease is uncommon in adult PiZZ patients. Six percent of male patients will develop cirrhosis at 40 to 50 years of age and 15% at 50 to 60 years of age (22-24).

e. Glomerular renal disease defined as mild microscopic hematuria and proteinuria occur in up to 15% of patients. The etiology is unclear but antigen-antibody complexes directed against the PiZZ protein have been found in the kidney. Serum creatinines in these patients are normal (25,26).

It is controversial whether heterozygote PiMZ patients are at an increased risk for developing emphysema. Several facts concerning the PiMZ phenotype are known:

a. Lung function in non-smoking PiMZ patients is the same as non-smoking controls up to age 50.

b. Lung function in smoking PiMZ patients usually shows a normal FEV_1/FVC ratio up to age 50.

c. Abnormalities in pulmonary function studies in PiMZ smokers are so slight compared to normal smokers that it is doubtful whether overall life span is shortened over smoking PiMM controls, although postmortem examination in PiMZ patients does reveal an increased incidence of panacinar emphysema (11, 27-30).

Several recent case reports have linked AAT deficiency with bleeding disorders, especially during infancy. A questionable association with panniculitis has also been reported (31-34).

LIVER PATHOLOGY

A PAS positive material is found in the smooth endoplasmic reticulum of all PiZZ patients. Fluorescent tagged antiserum to AAT categorizes this material as immunologically similar to AAT. This compound appears to be a precursor material. Little or no sialic acid is found in the material. It is believed that sialic acid is required for the excretion of AAT from the hepatocyte. Thus, the lack of sialic acid leads to the accumulation of the precursor material.

Another interesting hepatic finding has been an increased incidence of cirrhosis and hepatomas in PiZZ patients. Autopsy studies have revealed histologic evidence of cirrhosis in 50% of patients and hepatomas in up to 3%. As noted earlier, children may have a peculiar form of neonatal hepatitis presenting with a cholestatic clinical picture. (20,24).

THERAPY

Several modes of therapy are under investigation to correct severe alpha-1 antitrypsin deficiency and therefore improve elastase-antielastase balance. Research at the National Heart, Lung and Blood Institute and the NIH has provided a simple method for partially purifying alpha-1 antitrypsin from human plasma and administering it to patients. After parenteral administration, bronchial lavage has documented protective levels of this alpha-1 antitrypsin in twenty-one PiZZ human patients (40). This experimental treatment requires large volumes of human plasma and has to be repeated every five days. Genetic engineering may provide greater amounts of AAT at lower cost in the future, making it available on a wider scale (3,35).

Danazol, a derivative of testosterone, has been found to increase serum AAT levels by almost 50% in seven severely deficient patients, presumably through its anabolic action. This improvement in the protease-antiprotease balance theoretically may impede future progression of lung disease. Long-term prospective trials are needed to determine whether correction of elastase-antielastase balance (by increasing AAT) will truly stop progression of lung and liver disease(1).

Liver transplantations have been successfully performed in several children with chronic hepatic failure due to AAT deficiency (2). Adult AAT deficient patients usually die of their lung disease (20,24).

Current therapy is supportive and directed at minimizing the progressive loss of functional lung units. PiZZ patients should be told to stop smoking since smoke attracts leukocytes to the lung and inactivates AAT, thus aggravating lung damage. Pulmonary infections should be treated promptly and vigorously. All patients should receive pneumovax and influenza vaccinations.

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ASTHMA

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Asthma is a costly disease, not only from an economic point of view, but also in terms of morbidity and mortality. It accounts for over 3,000 deaths, hundreds of thousands of hospitalizations, several million patient visits, and hundreds of millions of dollars expended in health care resources annually in the United States. The prevalence of asthma varies with age and sex. In the United States, 2 to 5% of the adult population is affected while the incidence of childhood asthma has been placed at 11% with an apparent slightly greater prevalence among boys.

Reactive airway disease is classified into extrinsic and intrinsic asthma. In extrinsic asthma, bronchospasm is attributed to an immunologic response of the patient to an allergen. Extrinsic asthma occurs in atopic individuals who often have a strong family history for allergic manifestations, including asthma, hay fever, and urticarial eruptions. Serum IgE levels are typically elevated. Bronchospasm frequently appears in childhood and is manifested by dyspnea, cough, or wheezing. The bronchospastic response occurs promptly after exposure to a recognized allergen. Increased sputum production and peripheral eosinophilia are characteristic features. Intrinsic asthma typically occurs at a later age. An extrinsic allergen cannot be identified, and a family history for allergy usually is absent. Immediate skin test hypersensitivity to common allergens usually is negative, and IgE levels are normal. Attempts to classify reactive airway disease into these broad categories is difficult, however, since considerable overlap occurs among individual patients.

PATHOPHYSIOLOGY

Asthma is manifested by widespread narrowing of the airways that changes in severity, either spontaneously, or as a result of treatment. The reversible airway obstruction is caused by smooth muscle contraction and mucosal edema. Secretion clearance is diminished and production may be increased. Although the etiology of bronchial hyperreactivity is unknown, possible mechanisms include an increased responsiveness of the smooth muscle itself, an abnormality in the autonomic nervous system control of the smooth muscle or an increase in the accessibility of the stimulus to the target cells. An increase in airway wall thickness and smooth muscle mass probably contributes to the reactive state. Irritant receptors located in the airways, nose, larynx, and lungs respond to mechanical and chemical irritants resulting in reflex bronchoconstriction through vagal efferent pathways.

Bronchospasm results in several interrelated physiologic abnormalities listed in Table 1 including an increase in airway resistance five to six times above normal, prolonged expiratory time and reduced forced vital capacity. The forced expiratory volume in one second (FEV_1) is diminished as are the midexpiratory flow rate (MEFR) and the peak expiratory flow rate (PEFR). Hyperinflation is manifested by an increase in residual volume and functional residual capacity but diminished vital capacity and elastic recoil. Total lung capacity may be normal or only slightly increased. Ventilation-perfusion (V/Q) mismatching results in hypoxemia. An increase in airways resistance leads to progressive alveolar hypoventilation and hypercapnia with subsequent lactic acidemia secondary to the increased work of breathing.

PRECIPITATING FACTORS

Various factors and/or mechanisms may contribute to bronchospasm in the susceptible patient (Table 2). A predominant precipitating factor is respiratory infection, principally viral in origin. Allergic asthma is IgE mediated through mast cell mediator release. The triad of asthma, nasal polyps, and sensitivity to aspirin has been well recognized in a subpopulation of asthmatics for many years. Aspirin, other nonsteroidal anti-inflammatory drugs and tartrazine can produce bronchospasm within minutes to hours after ingestion. Nearly all nonsteroidal anti-inflammatory drugs have the potential to cause bronchospasm, apparently through their effects on prostaglandin synthesis via the cyclo-oxygenase pathway. Occupational asthma appears to be responsible for between 5 and 15% of asthma in the general adult population. Two major response patterns are noted: an immediate type, which begins and reaches its peak within minutes of the triggering stimulus, usually resolving within one to two hours; and the late type of asthmatic response, which is not clinically apparent for several hours after the stimulus and may require more than a day for complete recovery. Atmospheric pollutants play a major role in the exacerbation of symptoms in some asthmatics. Inhalation of sulfur and nitrogen oxides, hydrocarbons, and ozone as well as cigarette smoke can lead to significant bronchospasm in susceptible individuals. Sulfiting agents are used extensively, especially in restaurants, as preservatives in wine, beer, fruits, and vegetables, and when ingested can precipitate bronchospasm in certain asthmatics. Exercise-induced asthma appears to be related to respiratory heat exchange. Factors that promote heat loss include decreased temperature and humidity of inspired air and increased ventilatory frequency. Bronchospasm typically occurs at six to ten minutes after exercise begins and may worsen following completion of the exercise. Chronic, intractable asthma can result from gastroesophageal reflux. The bronchospasm appears to be vagally mediated. Conservative medical management of the reflux can result in a marked improvement in the bronchospasm. Sinusitis is an important precipitating factor in reactive airways disease. Bronchospasm may result from bacterial seeding of the lungs from the sinus drainage resulting in a secondary bronchitis and subsequent bronchospasm. Another proposed mechanism includes reflex bronchospasm mediated via the parasympathetic nervous system. In addition B-adrenergic blockade may be enhanced by the sinusitis. In patients with refractory asthma, sinus x-rays may reveal mucosal thickening and/or air fluid levels. Prolonged antibiotic therapy often results in radiographic clearing of the sinuses and clinical improvement in the bronchospasm. Occasionally surgical procedures may be necessary for optimal control.

ASSESSMENT OF BRONCHOSPASM

Assessment of the degree of bronchospasm is a critical first step in the evaluation of a patient with an acute exacerbation of asthma. Too often patients are released from the emergency room only to return over the next several hours or days with persistent bronchospasm. Careful history pertaining to the duration and course of the current attack is important, as is knowledge about prior bronchodilator therapy and use of corticosteroids, and failure to respond to previously effective therapy. In addition, a history of previous episodes requiring hospitalization and related illnesses or exposures may be helpful. Patients with severe bronchospasm frequently note tachyphylaxis to Beta-adrenergic agents.

Despite attempts to correlate multiple physical findings with the degree of bronchospasm, several studies have confirmed that the physical examination is insensitive. Nevertheless, the physical examination is an integral part of the clinical assessment of the patient with bronchospastic disease. A patient's general appearance often reflects the degree of bronchospasm. The absence of significant wheezing can be an ominous finding, reflecting severe flow obstruction with little air movement. Tachycardia, tachypnea, and fever may be present. Use of accessory muscles and intercostal muscle retractions suggest severe airflow obstruction. When present, a paradoxical pulse greater than 20 mm Hg reflects severe bronchospasm but may be absent in up to 50% of patients with severe flow obstruction.

Although usually normal, the electrocardiogram occasionally reveals P-pulmonale, supraventricular tachycardia, right ventricular hypertrophy, right bundle branch block or right axis deviation. Chest radiographs frequently demonstrate hyperinflation. Arterial blood gas measurements often are over-utilized in the assessment of bronchospasm, as their correlation with the degree of airway obstruction is poor. If the patient has a productive cough, examination of a gram-stained sputum sample may reveal dominant bacteria. Peripheral or sputum eosinophilia may reflect allergically-mediated bronchospasm.

The most effective and reproducible techniques to establish severity of airway obstruction are spirometric measurements and evaluation of expiratory flow rates. Repeat evaluation of the PEFR or FEV_1 can be used to direct therapeutic management. Measurement of the peak expiratory flow rate offers the advantage of not requiring a full expiration. Peak flow rate measured in liters per minute closely correlates with the spirometric measurement of the FEV_1, but like the FEV_1 is an effort-dependent maneuver that requires good patient cooperation and effort. The peak flow meter is relatively inexpensive and the results are reproducible. Severe obstruction in adults correlates with an FEV_1 of less than 1 liter or a PEFR of less than 100 L/minute. Specific improvement and projected successful outpatient management correlate with posttreatment PEFR values greater than 300 L/minute or an FEV_1 greater than 2.1 liters.

Indications for hospitalization include failure of the patient to respond to an adequate trial of bronchodilator therapy, including B-adrenergic agents and theophylline preparations. Patients who frequently require hospitalization include those previously treated with corticosteroids or whose current episode of bronchospasm has persisted more than 24 hours. Additional factors necessitating prompt hospitalization include an alteration in mental status, cyanosis, severe hypoxemia, hypercapnia, pneumothorax, or pneumomediastinum. Admission guidelines based on spirometry include an initial FEV_1 less than 30% of predicted and failure to improve by more than 35% after 60 minutes of bronchodilator therapy. A PEFR less than 100 L/minute reflects severe bronchospasm. Failure of PEFR to improve significantly after bronchodilator therapy identifies those who are unlikely to be managed successfully as outpatients. There are no clear-cut guidelines for deciding what constitutes an adequate response to therapy based on PEFR.

STATUS ASTHMATICUS

An episode of asthma that is refractory to bronchodilator therapy, including B-adrenergic agents and intravenous aminophylline, is known as status asthmaticus. This condition typically occurs in patients who are symptomatic for days or weeks. In some cases, patients gain intermittent, temporary relief from their bronchospastic symptoms with suboptimal courses of bronchodilator therapy that fail to completely reverse the underlying bronchospasm. Although respiratory failure generally develops over hours to days, life-threatening bronchospasm can occur within minutes. Spirometric and expiratory flow measurements in patients with status asthmaticus usually reveal severe flow obstruction. Mucus plugging, mucosal edema, and inspissated secretions account for the apparent resistance to bronchodilator therapy in patients with status asthmaticus.

MORTALITY

Asthma death rates have increased among both children and adults in the United States from 1979-1984. Mortality from asthma has also increased in other countries. The greatest abnormal increases recently have been among those more than 50 years of age. However, an increase in mortality rate of more than 60% has been noted among children between 1977 and 1980. Death from asthma is a particularly tragic occurrence because, in many cases, it appears to be preventable. Death can be sudden or follow a steady progression of the disease. Sudden deaths occur from peripheral vascular collapse and hypoxia, cardiac dysrhythmia, or, occasionally, adrenal insufficiency. Deaths in the 1960s were often attributable to the overuse of inhaled isoproterenol, with subsequent cardiac dysrhythmias, and delay by the patient in reaching appropriate medical care. Death now is attributed to several mechanisms (Table 3). The limited data available implicates undertreatment more often than overtreatment as a cause of death from asthma. To have an impact on the mortality rate early implementation of appropriate therapy is imperative. Unfortunately, inadequate medical management of asthma is common.

Delay in therapy occurs in patients who fail to recognize the severity of their attack. Medical mismanagement can occur in several stages in the treatment of the asthmatic patient. Reliance on the traditional clinical features in bronchospastic patients often results in significant errors in the assessment of airway obstruction. In addition, errors in medical management occur in the form of underutilization or overutilization of bronchodilators. A significant number of patients with severe asthma die before ever reaching the hospital because of the rapid progression of their disease. Finally, a clear association has been established between the use of sedatives during exacerbations of bronchospasm and asthma deaths.

GENERAL MANAGEMENT

The overall management of a patient in status asthmaticus requires close observation, bronchodilator therapy, enhancement of secretion clearance, and supplemental oxygenation as needed. As a general rule, oxygen may be safely administered by nasal cannula or face mask when needed as oxygen induced respiratory depression is rarely a major concern. Dehydration with subsequent mucus impaction may be a significant problem. The role of aerosol or ultrasonic nebulization is controversial. Aerosols have a direct irritant effect on the airways, and their deposition is unpredictable. Nonspecific irritants such as cold mist, when inhaled by the patient with asthma, may cause bronchial constriction through stimulation of irritant receptors in the airway. Mucolytic agents such as acetylcysteine have no

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documented beneficial effect on mucociliary clearance in patients with chronic pulmonary disease. Mucolytic agents may produce bronchial wall edema and bronchospasm. Intravenous fluid replacement should be judiciously regulated. Chest physiotherapy and deep coughing at regular intervals may occasionally loosen mucus plugs in the airway and enhance bronchial secretion clearance. Antibiotics are not used routinely unless evidence of bacterial infection is present. Intermittent positive pressure breathing (IPPB), inhaled corticosteroids, and cromolyn sodium are contraindicated in the treatment of acute asthma.

BRONCHODILATOR DRUG THERAPY

Bronchodilators act by relaxing bronchial smooth muscle and enhancing mucociliary clearance. Beta-2 adrenergic receptor stimulation results in increased cyclic AMP levels intracellularly, promoting bronchodilatation via bronchial smooth muscle relaxation, and inhibition of histamine release from mast cells. In addition, Beta-2 agonists cause vasodilatation, and enhance mucociliary clearance. These agents may be administered parenterally, orally, or by nebulization. An advantage of aerosol administration is that a much smaller dose is required, as the drug is applied selectively to the receptors in the airway. The recommended dose for metaproterenol (Alupent) is 0.2-0.3ccs in 2-3ccs normal saline nebulized every three-four hours. If Isoetharine (Bronkosol) is used 0.25-0.5ccs (1:200 soln) in 1.5-3.0cc normal saline should be administered every two hours as isoetharine has a shorter half-life. Albuterol 0.5% solution, 0.5 ml(2.5mg) in 2.5cc saline, administered every 6-8 hours has recently been approved for nebulization therapy.

METHYLXANTHINES

Theophylline and aminophylline have been an integral part of therapy for asthma for nearly 50 years. Inhibition of phosphodiesterase by theophylline is no longer thought to be the principal mechanism of bronchodilatation. Theophylline-mediated catecholamine release most likely plays a significant role in elevating cyclic AMP, thereby enhancing bronchodilatation. Pulmonary effects of theophylline include bronchodilatation, enhanced respiratory drive and bronchial mucociliary clearance, pulmonary artery vasodilatation, and inhibition of mast cell mediator release. In addition, theophylline increases diaphragmatic contractility and endurance, and appears to be of benefit to patients with respiratory failure. Synergism occurs between theophylline and the B-adrenergic receptor agonists, resulting in enhanced bronchial smooth muscle relaxation. The optimal therapeutic range is a serum theophylline concentration of 10-20 ug/ml. Serum half-life varies from 2.9 to 12.8 hours in adults and from 1.4 to 7.9 hours in children. Table 4 reflects factors affecting theophylline elimination. Guidelines for maintenance aminophylline infusion rates are based on the patient's age, smoking history, and other interrelated factors (Table 5).

Daily theophylline levels should be measured in order to adjust the maintenance infusion rate appropriately. The major determinant in the half-life of theophylline is hepatic metabolism. The half-life in children and smokers averages three hours, in the average adult 4.6 hours; and in some patients with coexisting medical illnesses up to 12 hours. The side effects due to theophylline toxicity include headache, insomnia, nervousness, abdominal discomfort, nausea and vomiting, hypotension, dysrhythmias, and seizures. These side effects increase as levels exceed 20 ug/ml.

CORTICOSTEROIDS

Corticosteroids are an effective, integral part of the therapy of patients with status asthmaticus. Corticosteroids are thought to have an early bronchodilator effect through the lowering of B-adrenergic receptor threshold responses to catecholamines. In addition, they possess a significant anti-inflammatory effect and may promote bronchodilatation by interfering with calcium-mediated bronchial smooth muscle contraction. It has recently been shown that methylprednisolone (125mg IV) given on presentation in the emergency room in addition to standard emergency treatment for asthma can prevent significant morbidity and reduce the number of hospitalizations. The optimal dose of corticosteroids in the treatment of status asthmaticus remains controversial. Many groups advocate a minimal initial dose of 250 mg methylprednisolone or its equivalent administered intravenously and repeated every four to six hours. The primary concern is that patient care may be severely compromised if corticosteroids are given in insufficient doses too late in the course of the asthmatic attack. As bronchospasm resolves, the intravenous corticosteroid dosage may be reduced and oral prednisone substituted.

ANTICHOLINERGIC AGENTS

Cholinergic receptors in the airway smooth muscle may cause smooth muscle contraction and bronchospasm stimulated through vagal efferent pathways. Anticholinergic agents actat the muscarinic receptors to inhibit acetylcholine, the neurotransmitter of the parasympathetic division of the autonomic nervous system. Nebulized atropine may be useful, especially when B-adrenergic agents and methylxanthines are unsuccessful in controlling asthmatic symptoms. Ipratropium bromide (Atrovent) is a derivative of atropine with low lipid solubility which limits its absorption across biologic membranes. It has relative bronchial selectivity with minimal systemic absorption when given by aerosol. Overall Atrovent appears to be equal or inferior to the B-adrenergic agonists in the treatment of asthma. Maximal bronchodilatation occurs slowly and it is only available in a metered-dose inhaler, thus its use in acute situations is limited.

CROMOLYN SODIUM

Cromolyn has been shown to inhibit histamine release from mast cells. Oral absorption is poor. It is administered by inhalation, either as a powder, an aqueous solution or via a metered dose inhaler. Advantages include lack of toxicity and effectiveness in preventing bronchospasm when properly used. Cromolyn has been found to be effective in preventing exercise-induced asthma. Powdered cromolyn should not be used during an acute exacerbation of asthma.

IMMUNOTHERAPY

Repeated injections of allergen extracts that cause an immediate skin reaction result in the production of "blocking" antibodies, which may decrease the late, but not the early, IgE mediated allergic response. Controversy persists concerning the use of immunotherapy in patients with allergically mediated asthma because of the lack of standardization of allergen extracts and dose, the lack of criteria for selection of those patients who might benefit, and the lack of objective studies to document its possible benefit in asthma. It seems reasonable to employ immunotherapy for selected patients with episodic wheezing associated with rhinorrhea following exposure to known allergens.

MECHANICAL VENTILATION

Mechanical ventilation is required in approximately 1% of patients in status asthmaticus. Precipitating factors include sedation, delays in gaining medical assistance by the patient, incomplete assessment of the degree of bronchial obstruction, underuse of corticosteroids, and rapidly progressive bronchoconstriction with respiratory failure. Mechanical ventilation is not therapeutic but rather supportive until bronchodilator therapy becomes effective. Indications for tracheal intubation and mechanical ventilation include progressive fatigue, depressed level of consciousness, respiratory acidemia with pH less than 7.20, refractory hypoxemia, cardiopulmonary arrest, progressive hypercapnia despite bronchodilator therapy, and overall clinical deterioration. Tracheal intubation in asthmatics entails considerable risks, including reflex bronchospasm from stimulation of the larynx and trachea. Nasotracheal intubation should be avoided in patients with nasal polyps in order to avoid hemorrhagic complications. High ventilator pressures frequently result from increased airway resistance. High flow rates and high tidal volumes should be avoided to minimize peak respiratory pressures. The high peak inflation pressures may induce profound hypotension and barotrauma. Sedation and neuromuscular paralysis are sometimes required. Positive end-expiratory pressure (PEEP) should routinely be avoided in patients with status asthmaticus.

In general, complications from conventional mechanical ventilation in the asthmatic patient are higher than in other disease states. Mortality for patients in status asthmaticus treated with mechanical ventilation ranges from 10 to 20%. The incidence of barotrauma also appears to be increased and is associated with a high mortality rate. A paradox in the management of the patient in status asthmaticus develops if concerns about complications of mechanical ventilation result in delay of initiation of required ventilatory support. Such inappropriate delay may contribute to an increased risk of mortality. The advantages of intubation and mechanical ventilation include control of ventilation and oxygenation in most cases, provision of rest for the fatigued patient, and possibly enhanced clearance of secretion by fiberoptic bronchoscopy. Bronchoscopy may provoke reflex bronchospasm. Lavage can be followed by increasing hypercapnia, bronchospasm, and laryngeal edema. Long term benefits from bronchoscopy are difficult to substantiate. Patients with extensive mucus plugging of both large and small bronchi may benefit from therapeutic lavage, however. In general, bronchial lavage should be considered a last resort in patients with mucus plugging refractory to conventional bronchodilator therapy and chest physiotherapy.

GENERAL ANESTHESIA

Potent general anesthetics have significant bronchodilator effects. Halothane and enflurane anesthesia may be considered for the patient in whom mechanical ventilation, sedation and paralysis, and maximum bronchodilator therapy are unsuccessful. Potential complications of halothane anesthesia include myocardial depression, cardiac dysrhythmias, and right-to-left intrapulmonary shunting.

CONCLUSIONS

Intensive treatment should be continued, even after the apparent clinical improvement of patients in status asthmaticus, because of persistent physiologic abnormalities of the smaller bronchi. Corticosteroids should be tapered over several weeks and bronchodilator therapy with methylxanthines and Beta adrenergic agents should be continued.

Reductions in asthmatic deaths ultimately will be achieved only when patients recognize the severity of their attack and seek medical assistance early. They should be instructed that the ineffectiveness of medications which previously have been effective, or a sudden change in clinical signs and symptoms, indicates serious disease. Utilization of a mini peak flow meter at home can identify significant airflow obstruction in patients with minimal signs or symptoms and may indicate the need for more aggressive bronchodilator therapy at an earlier, more responsive stage of bronchospasm.

Table 1

Asthma: Physiologic Changes

Increased airway resistance
Decreased specific conductance
Prolonged expiratory time
Decreased FVC, FEV_1, MMEF, PEFR
Increased RV, FRC
Diminished elastic recoil
Normal or increased TLC
V/Q mismatching

Table 2
Asthma: Precipitating Factors

Respiratory infection
Allergic reaction to inhaled antigen
Idiosyncratic reaction to aspirin or other NSAID
Occupational exposure
Environmental exposure (air pollution, metabisulfite ingestion)
Nonselective B-blocking agents (propranolol, timolol maleate)
Exercise
Mechanical stimulation (coughing, laughing, cold air inhalation)
Emotional stress
Inappropriate bronchodilator management
Reflux esophagitis
Sinusitis

Table 3

Factors in Asthma Deaths

Delay in therapy
Medical mismanagement (assessment/therapy)
Sedation
Bronchodilator toxicity
Rapidly progressive disease
Adrenal insufficiency
Infection

Table 4

Factors Affecting Theophylline Elimination

Factor	Inhibited Metabolism	Enhanced Metabolism
Age	Premature infant; possibly elderly	Age 1-16 years
Body habitus	Obesity	
Diet	Low-protein, high-carbohydrate diet; dietary methylxanthines (caffeine)	High-protein, low-carbohydrate diet
Smoking		Tobacco/marijuana
Disease States	Hepatic dysfunction CHF; pulmonary edema, pneumonia, acute febrile illness	
Drugs	Cimetidine; troleandomycin; erythromycin	Phenobarbital; phenytoin; isoproterenol

Table 5

Recommended Maintenance Doses of Intravenous Aminophylline for Treating Asthma*

Condition	Loading Dose (mg/kg)	First 12 Hr (mg/kg/hr)	After 12 Hr (mg/kg/hr)
Children and young smoking adults	6	1.0	0.8
Healthy nonsmoking adults	6	0.7	0.5
Adults older than 50 yr or with COPD	6	0.6	0.3
Adults with heart or liver disease	6	0.5	0.2

*From George R.B.: Arch. Intern. Med 142:933-936, 1982.

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BRONCHIECTASIS

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INTRODUCTION

Bronchiectasis is defined anatomically as persistent abnormal dilatation of bronchi that may be diffuse or localized. Once a common disease, the incidence of bronchiectasis has declined in association with the decline of tuberculosis, development of effective measles and pertussis vaccines and the use of broad spectrum antibiotics.

ETIOLOGY

The etiology for bronchiectasis usually falls into one of two categories: congenital anomalies, and acquired (usually infectious) etiologies. The list of congenital abnormalities associated with bronchiectasis includes Kartagener's syndrome, dyskinetic cilia syndrome, cystic fibrosis, Young's syndrome, hypogammaglobulinemia, Williams-Campbell syndrome and rarely alpha-1 antiprotease deficiency. Kartagener's syndrome consists of the triad of bronchiectasis, sinusitis and situs inversus. Bronchiectasis occurs in 15-25% of patients with situs inversus (1-4). Impaired mucociliary clearance increases the probability of pulmonary infection. The dyskinetic cilia syndrome is associated with sinusitis, otitis, recurrent bronchial infections, productive cough and frank bronchiectasis (5-8). Infections probably occur due to the delay in removal of infectious material from the bronchi, nose, sinuses and middle ear. Despite frequent pulmonary infections the rate of decline of pulmonary function is usually slow and the disorder is compatible with normal life expectancy (9,10). Cystic fibrosis or mucoviscidosis is commonly associated with bronchiectasis and is discussed in detail in the following chapter. Unlike most other forms of bronchiectasis which preferentially affect the lower lobes, involvement of the upper lobes is characteristic in patients with cystic fibrosis (11,12). Bronchiectasis is frequently seen in patients with disorders of humoral immunity. Deficiency of IgG is seen in patients with Type I dysgammaglobulinemia and variable hypogammaglobulinemia. Deficiencies of the IgG subclasses are associated with the recurrent pyogenic pulmonary infections which can lead to bronchiectasis (13-16). Deficiencies in cellular immunity as seen in the DiGeorge syndrome and severe combined immunodeficiency (SCI) are frequently associated with additional immunoglobulin deficits (17,18). Most cases of immunoglobulin deficiency can be detected by quantitative serum immune globulin determinations. The diagnosis of IgG deficiency in patients with bronchiectasis is important since the disease course may be significantly altered by regular injections of gamma globulin (19). Defects in complement components, particularly C_3, can lead to recurrent pyogenic infections (20). Alterations in the number or function of neutrophils may significantly impair pulmonary defenses against pyogenic bacteria, thereby leading to bronchiectasis. The Williams-Campbell syndrome is reflected by a deficiency of bronchial cartilage resulting in bronchiectasis (21-23). Alpha-1 antitrypsin deficiency is an autosomal recessive disorder that classically leads to pulmonary emphysema but can also rarely result in bronchiectasis (24).

Acquired bronchiectasis usually refers to airways that are diseased secondary to infection (i.e. tuberculosis, pyogenic pneumonia, pertussis, measles, or adenovirus). Localized bronchiectasis may be secondary to bronchial obstruction from neoplasm, mucous plugging, extrinsic lymph node compression, or foreign body aspiration. Childhood pneumonia secondary to measles, pertussis, or adenovirus can result in significant airway damage and subsequent bronchiectasis. Patients with allergic bronchopulmonary aspergillosis (ABPA) can develop localized bronchiectasis secondary to mucous plugging. The yellow-nail syndrome is a disorder associated with bronchiectasis, lymphedema, and yellow nails. The etiology is unknown (25).

PATHOPHYSIOLOGY

Bronchiectasis is associated with atelectasis, diffuse bronchitis and obliteration of smaller bronchi resulting in progressive respiratory insufficiency. Pulmonary manifestations are reflected by a diminished vital capacity, expiratory flow rates and maximum voluntary ventilation (MVV). Air trapping is manifested by increased functional residual capacity and residual volume. The diffusion capacity is occasionally diminished and hypoxemia results from ventilation-perfusion (V/Q) abnormalities and shunt. The severity of the dysfunction usually parallels the extent of bronchiectasis. Repeated lower respiratory infections accelerate the dysfunction and cor pulmonale may develop. Histologic examination of bronchiectatic lung demonstrates dilatation of the bronchi, substantial inflammation and destructive changes. The columnar epithelium may be ulcerated and replaced by hyperplastic squamous epithelium. Inflammatory cell infiltration and fibrous tissue deposition may be seen. Large anastamotic channels between bronchial and pulmonary vessels may develop resulting in an increase in bronchial arterial flow which presumably predisposes patients to develop hemoptysis.

CLINICAL PRESENTATION

Patients with bronchiectasis present with a history of recurrent bronchopulmonary infections. They frequently note voluminous sputum production with symptoms often dating back to childhood. Occasionally patients experience hemoptysis in association with the purulent sputum or as an unexpected event in an otherwise asymptomatic patient with previously unrecognized bronchiectasis. This form of the disorder known as "dry bronchiectasis" is frequently the sequella of previous tuberculosis. Occasionally patients present with symptoms consistent with chronic obstructive pulmonary disease (COPD) and/or cor pulmonale. On physical examination, crepitant rales are heard over the affected lobes or segments and clubbing is relatively common (26).

Roentgenographic findings are nonspecific, seldom diagnostic, and may rarely be normal. The chest x-ray may demonstrate increased lung markings, honeycombing, atelectasis, or pleural changes.

DIAGNOSIS

Bronchography provides a morphologic diagnosis and objective assessment of the degree of pulmonary bronchiectatic involvement. Reid developed a morphologic classification of bronchiectasis that is useful when bronchography is utilized (27). There are three basic morphologic classifications of dilatation: cylindrical, saccular, and varicose. Cylindrical dilatation of the bronchi may occur transiently following episodes of pneumonia and has been termed "reversible" bronchiectasis (28-30). A decision to remove a bronchiectatic lobe or segment should not be based on cylindrical changes seen on bronchograms performed during the first four months following an episode of pneumonia (26). Bronchograms of patients with cylindrical bronchiectasis demonstrate failure of the lumina to taper normally, but there is no increase in diameter peripherally. In varicose bronchiectasis, the bronchi show irregular constrictions and dilatation. Saccular bronchiectasis is present when the bronchi terminate in large, ballooned, grape-like clusters. The presence of varicose and saccular bronchiectasis usually implies irreversibility (31). Computed tomography may provide a useful noninvasive alternative to bronchography. With thin sections (1.5mm cuts), moderately severe grades of bronchiectasis may be detected, but mild cylindrical bronchiectasis may be missed. If CT findings are equivocal or when surgery is being contemplated, bronchography should be performed (39,40).

TREATMENT

The general principles of bronchiectasis therapy include facilitation of excessive secretion removal, infection control and good nutrition. Secretion removal may be enhanced in patients with excessive sputum production by using chest percussion and postural drainage (32). There have been no clear benefits associated with aerosol therapy. Bronchodilators may be useful in patients with obstructive lung disease. Infection control is crucial. All appropriate immunizations should be administered including measles, pertussis, influenza and pneumonia vaccines. Exacerbations of bacterial bronchitis or pneumonia in patients with bronchiectasis should be treated with full doses of antibiotics as determined by sputum flora sensitivity. It is reasonable not to treat the asymptomatic or minimally symptomatic patient except during exacerbations and to consider continuous therapy only for those patients with persistent symptoms or frequent exacerbations. Outpatient antibiotic management is similar to that of patients with chronic bronchitis. In patients who present with hemoptysis, antibiotics are empirically used to treat any underlying infection. Localization of the bleeding site via bronchoscopy and/or angiography is indicated when bleeding is significant. Occasionally patients require surgical resection of the affected lobe if bleeding is massive.

Surgical resection of bronchiectatic pulmonary segments has been the traditional standard therapy (33-38). Improved medical therapy and conservative management with antibiotics have markedly reduced the need for surgical intervention. Current indications for surgical management include poorly controlled symptoms (persistent hemoptysis), localized disease, absence of an underlying generalized disorder (e.g. cystic fibrosis, hypogammaglobulinemia), absence of diffuse bronchitis/emphysema, and acceptable pulmonary reserve. Patients with extensive disease may not benefit from surgical management. Preoperative bronchography may be important to confirm localized disease as chest roentgenograms may be misleading (38).

PROGNOSIS

Patients with diffuse bronchiectasis associated with underlying cystic fibrosis or an immunologic deficiency may have a poor prognosis while those patients with asymptomatic localized bronchiectasis discovered on incidental chest roentgenogram usually have clinically insignificant disease with no effect on life expectancy. Prior to antibiotic therapy the average duration of symptoms prior to death was 5 years and the time from diagnosis to death 2 years. Today with improved conservative medical management and careful patient selection for surgical intervention, the overall outlook for patients with bronchiectasis is very good.

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CYSTIC FIBROSIS IN ADULTS

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INTRODUCTION

Cystic fibrosis was first formally described in 1938 as a disease which in its most florid form presented in young children as severe progressive pulmonary or pancreatic insufficiency. Since then increasing experience has shown cystic fibrosis to be a protean disease with clinical presentations of variable severity. Cystic fibrosis is the most common lethal genetic disease in Caucasians. There is a 5% carrier rate in the Caucasian race and an incidence of one per 2,000 live births in the United States. It is inherited as an autosomal recessive trait with no discernible linkage to blood group or HLA type. The variability and clinical severity of cystic fibrosis was originally attributed to a single allele which displayed variable penetrance. Evidence is now mounting, however, that cystic fibrosis may be coded by multiple alleles at the same genetic focus such that any two together will cause the characteristic abnormalities, with the severity determined by which alleles are present (1). Recently it has been discovered that the gene responsible for cystic fibrosis is located on chromosome 7. (Porteuous DJ, Trends in Genetics, June 1986)

RISK ASSESSMENT

This can be estimated by calculating the frequency of a gene in a two allele system according to the Hardy-Weinberg equation:

$$(p + q)^2 = 1$$
$$p^2 + 2pq + q^2 = 1$$

FF = p^2 = homozygous dominant
Ff = pq= heterozygote
ff = q^2 = homozygous recessive

As mentioned previously, the homozygous ff incidence is 1 in 2000 or 0.005 = q^2. Frequency of heterozygous state = .043 = 4.5% = 1 in 20 and of FF = 0956 = 95.6%. Therefore parents of a child with CF must both be heterozygous and siblings of the patient have a 50% chance of being heterozygous. The risk of carrying a gene is the product of the risks carried by each spouse.

e.g. a. chance that any two unrelated spouses are heterozygotes = 1/20 x 1/20 = 1/400

b. chance that a child born to two unrelated spouses will have CF - 1/400 x 1/4* = 1/1600

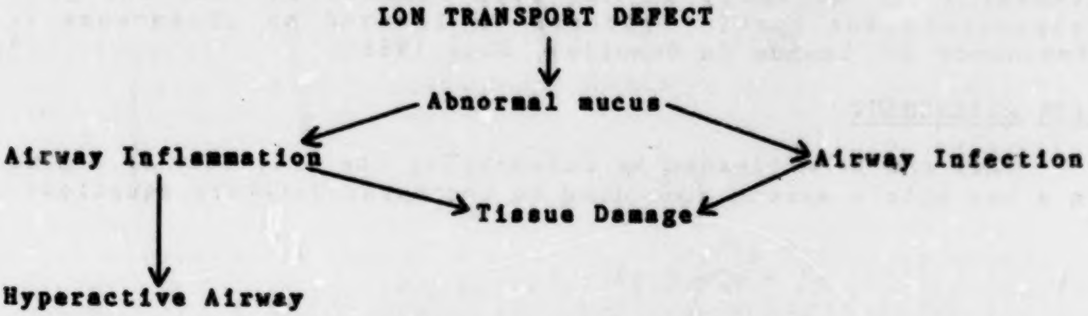
*1/4 = chance that two heterozygous parents will have a CF child.

PATHOPHYSIOLOGY

Cystic fibrosis is a generalized systemic disorder in which mucus secreting glands throughout the body secrete a dehydrated mucus which congeals in the ductule lumens. It is known that the lungs are normal at birth and that inflammation appears to begin in the small airways and progresses to involve the large bronchi. Over time the inflammation leads to the development of bronchiectasis. Emphysema does not appear to play a prominent role in the pathogenesis of this disease.

The overall pathophysiology appears to start with an ion transport defect which leads to production of abnormal mucus and eventually to airway infection, tissue damage and bronchiectasis (see Figure 1).

FIGURE 1



There are a large number of clinical and scientific studies which have attempted to clarify the pathogenesis of CF and its classical manifestations, but no unifying abnormality has been elucidated. The following factors have been analyzed, with studies available supporting and contradicting most:

1. Hypertonic secretions change viscoelastic properties of mucus.
2. A thinner periciliary fluid layer affects mucociliary clearance.

3. An increased negative potential difference exists across membranes favoring bacterial colonization.

4. Abnormal mucus leads to infection.

5. Infection promotes mucus abnormality.

6. Abnormal mucus leads to airway inflammation.

7. Inflammation in airways produces abnormal mucus.

8. Infection results in inflammation.

9. Inflammation leads to tissue damage.

10. Infection in airways leads to tissue damage.

11. Tissue damage results in infection and inflammation.

(Cystic Fibrosis. In Seminars Respiratory Disease, 1985 Vol 6 #4, 243-332)

The abnormality in cystic fibrosis may involve abnormal calcium homeostasis as local organ involvement is marked by increasing calcium concentrations. Calcium decreases the solubility of glycoproteins in saliva and mucus.

The sweat electrolyte defect may be explained by a sodium-reabsorption-inhibitory factor present in sweat and saliva. Its action has been demonstrated by transferring the pathologic secretion to a normal animal salivary or human sweat gland and reproducing classic cystic fibrosis electrolyte defects (18).

The ciliated epithelial surfaces are affected in some fashion as to preclude normal ciliary beat (1). The mucociliary clearance in patients with cystic fibrosis is decreased, possibly due to the production of a cilio-toxic factor. Several abnormal proteins produced in cystic fibrosis glandular secretions have cilio-toxic activity (10,18).

Patients with cystic fibrosis and their parents may also suffer from autonomic dysfunction manifested as increased cholinergic, increased alpha adrenergic, and decreased beta adrenergic responses. Fifty percent of patients have been shown to exhibit airway reactivity to histamine or methacholine with a prevalence of airway reactivity to exercise of 20-25%. (ARRD 1984; 129:911).

CLINICAL PRESENTATION

TABLE 1. *Clinical and Laboratory Presentations of Cystic Fibrosis*

NEWBORN	INFANCY	CHILDHOOD	ADOLESCENT/ADULT	ALL AGES
Meconium ileus: ileal atresia, volvulus, perforation and peritonitis, intra-abdominal calcifications Obstructive jaundice Meconium plug syndrome	Failure to thrive Prolonged bronchiolitis Right upper lobe atelectasis *Staphylococcus aureus* Staphylococcal empyema Hypogammaglobulinemia Metabolic alkalosis Hypoproteinemia, edema and anemia triad Hypoprothrombinemia and hemorrhage (hypovitaminosis K) Increased intracranial pressure (hypovitaminosis A) Rectal prolapse Salty taste	Hypoelectrolytemia Heat prostration Intussusception Nasal polyps Chronic secretory otitis media Palpable right lower quadrant fecal mass Pancreatic lithiasis Mucosal filling defects of large and small bowel by barium contrast Hydrocele and inguinal hernia	Aspermia in males Chronic cervicitis Infertility in females Delayed sexual development Glucose intolerance (abnormal GTT) Diabetes mellitus requiring insulin Pneumothorax Hemoptysis Kyphoscoliosis Osteoporosis Cholelithiasis Hypertrophic osteoarthropathy Acute pancreatitis Hypersplenism Reactive airway disease	Elevated sweat electrolytes Mucoid *Pseudomonas aeruginosa* Chronic cough Bronchiectasis Bronchitis Pneumonia Atelectasis Hyperinflation Cor pulmonale Clubbing Pancreatic insufficiency with malabsorption Nasal polyps Pansinusitis Meconium ileus equivalent/fecal impaction Small gallbladder Absent vas deferens

From Holsclaw "CF: Overview and Pulmonary Aspects in Young Adults" Clin Chest Med 1(3):407, 1980.

Adult patients with cystic fibrosis can be divided into two categories:

a. those with childhood cystic fibrosis who survive into adulthood.

b. those with symptoms too mild to suspect the diagnosis in childhood who manifest their GI and/or pulmonary disease in adulthood (2).

The first category of cystic fibrosis patients have an established diagnosis and treatment regimens when first presenting to an internist or pulmonologist. The second category accounts for about 10% of adult cystic fibrosis patients over the age of 25 years (1). The diagnosis of cystic fibrosis is important to establish in these adults for several reasons:

a. Patients with unrecognized cystic fibrosis may receive inappropriate antibiotics, since infection is usually caused by *S. aureus* and *P. aeruginosa*. The latter often arises after inappropriate antibiotic therapy.

b. Patients with unrecognized cystic fibrosis may undergo inappropriate surgery for bronchiectasis, inappropriate because it is a progressive rather than localized disease.

c. Patients with unrecognized cystic fibrosis have different complications from patients with COPD.

DIAGNOSIS

A diagnosis of cystic fibrosis should be suspected in any patient presenting with:

a. Obstructive lung disease during the first three decades.

b. Obstructive lung disease out of proportion to smoking history.

c. "Asthma" *and* clubbing

d. Sputum cultures positive for mucoid *Pseudomonas*

e. Lung disease along with disease of the pancreas, GI tract, etc.

f. Lung disease and family history of cystic fibrosis.

The chest x-ray in cystic fibrosis can show a wide range of abnormalities with the earliest and most common finding being apical interstitial disease which is classically worse in the right upper lobe. Adult patients have an equal prevalence of "interstitial" and cystic honeycombing patterns. Hyperinflation is less common and rarely some patients present with transient nodular infiltrates (1,17).

Cystic fibrosis is characterized by a progressive decline in pulmonary function. The earliest change is an uneven distribution of ventilation with resulting hypoxemia. Spirometry initially shows small airway obstruction followed by hyperinflation and air trapping. Later pulmonary fibrosis develops and leads to a restrictive component (17).

The respiratory flora in cystic fibrosis is unique. Frequently mucoid strains of *Pseudomonas* are isolated, usually of the serotype Homma-8. The finding of mucoid *Pseudomonas* in sputum from a young adult with lung disease should raise suspicion for undiagnosed cystic fibrosis.

Sweat chlorides remain the only reliable method of confirming the diagnosis of cystic fibrosis. This test should be done only by laboratories which have extensive experience with the procedure of pilocarpine iontophoresis. A minimum amount of 100gms of sweat should be collected. Although false positives and false negatives do occur, they are rare and are usually secondary to technical error. False negatives can occur in edematous states and false positives in cases of adrenal insufficiency, hypothyroidism and malnutrition. In children a value greater than 60 meq/l is diagnostic of cystic fibrosis. In adults the diagnostic level is above 80 meq/l. Values within 20 meq/l less than the diagnostic levels are highly suspicious and bear repeating (2). The sensitivity and specificity of the test in the diagnosis of cystic fibrosis is as follows:

Cl^- conc 60-130 meq/L = CF; Sens 98%, *96% in adults
Cl^- conc 50-60 meq/L = 1-2% CF patients
Cl^- conc 50 meq/L = 1/1000 patients

*Cl^- increases with age (ARRD 1983, 128:34-37)

The new diagnostic classification for cystic fibrosis as suggested by Stern and modified by Scoggins includes 3 major and 3 minor criteria. Diagnosis requires 3 major or 2 major and 3 minor criteria from a different organ system.

TABLE 2

Expanded Diagnostic Criteria for Adult Cystic Fibrosis

Major Criteria

1. Sweat-chloride concentration above 60 mEq/liter before age 20 and above 80 mEq/liter in an adult

2. Idiopathic chronic obstructive pulmonary disease

    a. nonsmoker

    b. upper lobe predominant cystic bronchiectasis

    c. exclusion of alpha-1 antitrypsin deficiency, dyskinetic cilia syndrome, tuberculosis, eosinophilic granuloma, sarcoidosis, immunoglobulin deficiency, or Young's syndrome.

3. Chronic *Pseudomonas aeruginosa* or *Staphylococcus aureus* bronchitis.

4. **Idiopathic obstructive azoospermia**

5. **Family history of cystic fibrosis**

Minor Criteria

1. **Pansinusitis, or nasal polyposis without allergy**

2. Digital clubbing

3. Asthma with a persistently abnormal chest radiograph

4. Spontaneous pneumothorax

5. Unexplained intestinal obstruction

6. Exocrine pancreatic insufficiency

7. Recurrent acute pancreatitis

8. Idiopathic biliary cirrhosis

DIFFERENTIAL DIAGNOSIS

Disease entities or clinical conditions which can present in a similar fashion to cystic fibrosis are noted in Table 3.

TABLE 3

Respiratory

Asthma
Chronic bronchitis
Bronchiectasis
Emphysema
Tuberculosis
Eosinophilic granuloma
Sarcoidosis
Alpha-1 AT deficiency
Dyskinetic cilia syndrome
Agammaglobulinemia
IgA deficiency
Young's syndrome
Ankylosing spondylitis

Gastrointestinal

Inflammatory bowel disease
Infectious enteritis
Gluten-sensitive enteropathy

COMPLICATIONS OF CYSTIC FIBROSIS

1. Pulmonary

Spontaneous pneumothorax occurs in approximately 16% of adult cystic fibrosis patients. Those patients usually have severe airflow obstruction (FEV$_1$ <50% predicted) and have an average recurrence rate of 50% with an overall mortality of 30%. Mortality however is more a reflection of the severe underlying parenchymal disease than of the pneumothorax itself. Pneumothoraces occur with equal frequency on either side and, in contrast to spontaneous pneumothoraces, there is no male predominance. Treatment for symptomatic patients includes tube thoracostomy, usually followed by either pleural sclerosis or thoracotomy for pleurodesis or partial pleurectomy. Table 4 summarizes outcome of treatment of pneumothorax in cystic fibrosis patient as reported in the literature.

Table 4 Outcome of Treatment of Pneumothorax in CF Patients

Reference (Place, Date)	No. Patients/ Population Surveyed	Incidence %	Episodes of Pneumo-thorax	Recurrences/No. Patients Treated by Each Method (% Recurrence Rate)				Mortality
				Observation	Closed Thoracotomy	Sclerosis	Pleurectomy*	
Boat et al[8] (University of Minn; NIH 1969)	15/400	3.8	32	2/8 (25%)	catheter: 3/7 (43%) tube: 7/20 (35%)	1/3 (33%)	None	20% before treatment 47% at 6 mo
Stowe et al[10] (Cleveland, 1975)	29/665	4.4	47	6/14 (42%)	14/20 (70%)	2/8 (25%)	0/5 (0%)	50% at 6 mo
Luck et al[9] (Chicago, 1977)	18/280 +4 adults	6.4	44	14/18 (77%)	12/25 (50%)	0/3 (0%)	0/3 (0%)	60% at 3 yr
Knight and Batten[2] (London, 1980)	36/152	23	71	8/20 (40%)	24/29 (83%)	4/8 (50%)	5/14 (36%)	NS†
McLaughlin et al[11] (Boston, 1982)	65/663	9.8	170	20/33 (60%)	needle: 11/14 (79%) tube: 41/65 (63%)	10/22 (47%)	0/16 (0%)	48% at 3 yr, 60% at 12 yr

* Pleurectomy frequently accompanied by pleurodesis and oversewing blebs; specific breakdown not available in each series
† NS = not specified

(References Bart et al, JAMA 209:2498, 2969; Stowe JM et al, ARRD 111:611, 1975; Luck SR et al, J. Thoracic Cardiovasc Surg 74:834, 1977; Knight et al, Perspective in Cystic Fibrosis 376, 1980; McLaughlin et al, J. Pediatrics 100:863, 1982).

In general, sclerosis is attempted first with open pleurectomy reserved for patients with acceptable pulmonary reserve and recurrence of pneumothoraces.

Significant hemoptysis is seen in approximately 7% of patients with cystic fibrosis and usually occurs with worsening of pulmonary infection. Massive hemoptysis carries a high mortality since it usually occurs in patients with poor pulmonary reserve.

Other pulmonary complications include lobar atelectasis, rhinosinusitis, nasal polyposis and cor pulmonale.

2. Gastrointestinal

The most frequent organs involved are the pancreas, intestines and liver.

Pancreatic insufficiency with symptoms of frequent bulky, foul-smelling stools and abdominal cramping is infrequently seen in adults. However lesser degrees of malabsorption can be present necessitating enzyme replacement. It has been demonstrated that adult patients with normal pancreatic function tend to have lower levels of sweat Cl- and a more favorable pulmonary prognosis. Episodes of acute pancreatitis are more common in adult patients with CF than in children.

Intestinal obstruction is seen in approximately 17% of adult cystic fibrosis patients, its incidence increasing with age. It becomes a recurrent problem in 50% of patients affected. The two most common precipitating factors are fecal impaction and intussusception. Cystic fibrosis patients also have a higher incidence of cholelithiasis, cholecystitis, appendicitis and periappendiceal abscess.

Liver function abnormalities are seen in 25% of cystic fibrosis patients, with focal biliary cirrhosis seen in 25% of patients, and multilobular cirrhosis in 2-5%. Progressive cirrhosis is the second most common cause of death, following pulmonary insufficiency. Approximately 15-30% of adults with cystic fibrosis will develop a fatty liver in association with malnutrition.

3. Musculoskeletal

In only a small proportion of adult patients with cystic fibrosis will clubbing of the fingers be absent. These tend to be patients with a history of mild suppurative pulmonary disease. Hypertrophic osteoarthropathy is also frequently observed in adults with cystic fibrosis. Rickets and osteomalacia may be caused by chronic malabsorption and malnutrition.

4. Renal

The only renal abnormalities seen in cystic fibrosis are decreased free water excretion and, of more importance, an increased clearance of aminoglycoside antibiotics. Rarely, secondary amyloidosis due to chronic suppurative pulmonary disease causes nephrotic syndrome.

5. Endocrine

Adults with cystic fibrosis can develop glucose intolerance due to insulin and glucagon deficiency produced by pancreatic fibrosis. In addition some patients may suffer from insulin receptor abnormalities or decreased sensitivity to insulin leading to an insulin resistent state.

Infertility is a common problem in both males and females afflicted with cystic fibrosis. Obstructive azoospermia in males is caused by poor development of the epididymis, vas deferens and seminal vesicles. It is stated that <3% of male patients with documented cystic fibrosis are fertile. Other abnormalities found in semen of male cystic fibrosis patients are low pH, low fructose and high citric acid levels which may also impair sperm function.

Females with cystic fibrosis also tend to have fertility problems even though their reproductive tract is anatomically normal. Potential causes for infertility include chronic illness and malnutrition, chronic cervicitis, frequent anovulatory cycles, and presence of thick cervical mucus which serves as a barrier to sperm penetration into the uterine cavity. Despite these changes, pregnancy can occur in cystic fibrosis. Approximately 12% of mothers die within six months of delivery and it is not uncommon for pregnancies to be complicated by congestive heart failure, premature delivery and fetal death.

6. Psychosocial

Like most chronically ill patients, patients with cystic fibrosis suffer from frequent depression and social maladjustment. Issues frequently faced by these patients are impending death, sexuality, marriage difficulties, financial burden of medical care and others. (Scoggins C., Respiratory Medicine Practice, Vol 1 #1, 1987).

PROGNOSIS

Cystic fibrosis was thought to be universally fatal by age 2-3 prior to 1939. While this was largely artifactual due to inadequate diagnosis, the overall outlook has substantially improved; survival to age 20 is now seen in approximately 50% to 70% of patients, provided appropriate and aggressive therapy is given (4). Cystic fibrosis appears to progress at a faster rate in females than in males for unknown reasons. Females have a poorer survival than males, and analysis of pulmonary function test performance decrement shows an average decline in the FEF25-75 in females of 9% a year, as compared to males who experience a decline at a rate of 7% per year (5).

Various clinical scoring systems have been established to help predict survival in patients with cystic fibrosis. The most useful of these was published in 1973 by Taussig and Di Sant'Agnese and considered factors such as pulmonary functions and general complications of the disease in 73 patients (6). A perfect score was 100 and severe disease correlated with scores of 50 or less. Mortality was as follows:

TABLE 5

MORTALITY IN PER CENT

Clinical Score	Three Years	Six Years
91-100	0	0
81-90	5	15
71-80	13	33
61-70	25	85
51-60	67	100
Less than 50	100	--

TREATMENT

A. Treatment of Pulmonary Manifestations

1. Infection -- *Staphylococcus aureus* and nontypable *Hemophilus influenzae* are the early sputum colonizers, subsequently followed by mucoid *Pseudomonas aeruginosa* strains late in the course. Outpatient management includes treatment with cephalexin or dicloxacillin for staphylococci; Septra or ampicillin for *Hemophilus influenzae*; and chloramphenicol for *Pseudomonas*. If inpatient therapy is required, oxacillin, an anti-pseudomonal penicillin and gentamicin should be given intravenously for no less than 14 days. Therapy should be directed by sputum cultures and sensitivities (7). Aerosolized antibiotics are still controversial. Four clinical studies demonstrate improved pulmonary function or decreased rate of infection but no absolute recommendation for their use exists. Table 6 summarizes 3 of these studies.

Table 6. Controlled Studies of Inhaled Antibiotics in Cystic Fibrosis

Study	Drug	No. Patients and Age	Sputum Culture	Results of Study
Double-blind randomized cross-over trial: 6 months drug, 6 months placebo[14]	1 gm carbenicillin plus 80 mg gentamicin or placebo twice daily	[illegible] patients aged 13–42 years	P. aeruginosa	1. [illegible] 2. Increase in FEV_1, [illegible] 3. Decreased frequency of hospital admissions
Two-year randomized prospective study[15]	Inhaled cephaloridine 500 mg two to three times daily plus oral cloxacillin or 0 inhaled cephaloridine plus oral cloxacillin	21–25 patients/group with mild to moderate lung disease	No chronic carriers of S. aureus; 90% had P. aeruginosa; 40% had P. capacia	1. Decreased acquisition and carriage of H. influenzae 2. No effect on number of respiratory illnesses, hospital admissions, clinical scores, roentgenographic scores, pulmonary function tests.
Prospective study: time on protocol 4–24 months[16]	80 mg tobramycin plus 1 gm ticarcillin twice daily	15 patients aged 4 to 30 years with moderate to moderately severe lung disease	P. aeruginosa	1. Decreased hospital admissions 2. No change in FEV_1

(Hodson ME et al Lancet 2:1137-1139, 1981; Nolan G et al. J of Pediatrics 101:626, 1982; Wall MA et al Cystic Fibrosis Club Abst 25:33, 1984).

In general, mild exacerbations are treated with specific oral antibiotics for at least 14 days. If the patient does not improve after a course of oral antibiotics or initially is very ill, hospitalization for IV antibiotics (at least two) for a minimum of 14 days (ARRD 1982, 126:31-36) is the standard treatment. When disease becomes severe, the patient may need to be maintained on continuous oral antibiotics.

2. Enhancing mucociliary clearance -- Percussion and postural drainage is universally applied to patients with cystic fibrosis, however its benefits are somewhat controversial. One study showed mild improvement in lung volumes and more rapid mobilization of sputum using percussion and postural drainage compared to controls (8). Another study has demonstrated increased maximal expiratory flow rates after postural drainage (9). Whether or not these small improvements in pulmonary function have clinical significance has yet to be demonstrated. Methylxanthines and beta agonists enhance mucociliary clearance and aid in reversing bronchospasm (10,11). Mist tents are no longer recommended. Mucomyst may be of value in selected patients but may cause bronchospasm (12,13,14).

3. Bronchoscopy -- Bronchoscopy is useful in localizing hemoptysis in patients with cystic fibrosis in addition to being used acutely to clear mucus plugs in the treatment of lobar atelectasis (1). In addition, Fogarty catheter endobronchial tamponade via bronchoscopy has been effective in the management of massive hemoptysis. (Saw EC, et al., Flexible fiberoptic bronchoscopy and endobronchial tamponade in the management of massive hemoptysis, Chest 70:589, 1976; Porter, DK et al, Massive hemoptysis in cystic fibrosis, Arch Intern Med 143:287, 1983)

4. Surgery -- Pleurodesis may be indicated for the treatment of recurrent pneumothoraces. The patient with massive hemoptysis may require pulmonary resection if the following criteria are fulfilled:

a. Failure of medical management including intensive antibiotic therapy.

b. Adequate pulmonary reserve

c. Precise localization of the bleeding site by either bronchoscopy or bronchial angiography.

* Those not considered surgical candidates can be managed by arteriography with bronchial artery embolization.

5. Ventilators -- A study by Davis and DiSant'Agnese reveal that only 6% of patients with cystic fibrosis placed on a ventilator for respiratory failure survived over one year. This subgroup demonstrated mild to moderate pulmonary function test abnormalities and had reversible causes of respiratory failure such as pneumonia. The study recommended that patients with severe end-stage cystic fibrosis who have shown progressive decline despite maximal medical therapy should not be placed on a ventilator as 69% will die while on ventilator therapy, 16% will die within 6 weeks of coming off the ventilator, and another 9% will be dead within one year (15).

6. Corticosteroids - Patients with cystic fibrosis have demonstrated increased levels of immune complexes in their respiratory tracts, especially those chronically infected with Pseudomonas species. Those patients having normal or low levels of serum IgG have a better prognosis. In a recent study, children treated with corticosteroids did better with regards to functional status and lung function than those not receiving the drug. Steroids can also be of benefit in the treatment of bronchospasm and in the treatment of allergic bronchopulmonary aspergillosis.

7. Oxygen - Patients with cystic fibrosis and progressive disease eventually develop resting hypoxemia or arterial oxygen desaturation with exercise. As in COPD, oxygen should be prescribed in the hope of preventing or slowing the progression of cor pulmonale.

8. Vaccines - Influenza vaccine is recommended yearly in these patients, with amantadine prophylaxis instead if a contraindication to vaccine exists. The efficacy of the pneumococcal vaccine is questionable but should probably be administered.

B. Miscellaneous (1)

Nutrition is extremely important and should be maximized by sufficient calories, pancreatic enzyme preparations, and cimetidine which enhances the effectiveness of the enzyme supplements. Normal body anthropomorphic measurements should be maintained. As noted earlier, intestinal obstruction from either fecal impaction or intussusception occurs in approximately one-quarter of patients with cystic fibrosis and will usually respond to conservative treatment including hydration, laxatives and gastrografin enemas. Surgery is usually not required. Heat prostration due to excessive sodium chloride losses via sweating can occur in patients with cystic fibrosis, especially in hot, arid climates. Bleeding from esophageal varices can be treated in the usual manner including selective splenorenal shunts with reasonably good results. Pancreatitis and diabetes mellitus may also occur and respond to standard therapy.

The specter of chronic disease and premature death places an intense emotional burden on the patient afflicted with cystic fibrosis. Survival and quality of life in these patients are in some part dependent upon their willingness to comply with a time-consuming and somewhat laborious medical regimen. To be effective in his care of the patient, the physician must recognize and deal with the psychological as well as the physical aspects of the disease.

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OBSTRUCTIVE SLEEP APNEA

Jay T. Segarra, Major, USAF, MC

HISTORICAL PERSPECTIVES

The first clinical description of the sleep apnea syndrome was provided by Charles Dickens in the "Posthumous Papers of the Pickwick Club". The "fat boy, Joe" is described as obese ("...twenty stun", i.e. 280 lb), gluttonous (" ...a young boa constrictor"), polycythemic ("...ruddy complexion"), a loud snorer ("...the snoring of the fat boy penetrated in a low and monotonous sound from the distant kitchen..."), and suffering from both cor pulmonale ("...young dropsy...") and personality changes ("...at times, he is a little deranged...").

This excellent vignette remained unrecognized as a clinical entity until the 1950's, and even then, as the 'Pickwickian Syndrome', was relegated to the status of a rare oddity in medical texts. All this changed about 15 years ago, however, with the investigations by Block, Sackner, and others (1) into the etiology for an alarmingly high incidence of silent nocturnal death in obese middle-aged and elderly men. Overnight tracings of respiratory effort via 'pneumobelts' placed around the chest and abdomen demonstrated a recurring cycle of four breaths, followed by a minute or so of no breathing--in other words, SLEEP APNEA. Subsequently, cinepharyngograms (sequential lateral x-rays of the upper airway) demonstrated the collapse of the upper airway and obstruction by the tongue during these apneic periods. These early observations led to an explosion of research in sleep apnea syndromes.

SLEEP ARCHITECTURE

Sleep consists of two major phases, non-REM and REM (Rapid Eye Movement). Each of these phases in turn is subdivided into stages. Stage 1 is a transitional stage between wakefulness and sleep, lasting 1/2 to 7 minutes. Hypnogogic jerks are common during this phase. Stage 2 is heralded by the appearance of 'sleep spindles' and 'K-complexes' on EEG. During this stage 'normal' individuals will experience occasional brief apneas, periodic breathing, and modest fluctuations in airway smooth muscle tone (2). Stages 3 and 4 constitute 'slow-wave sleep', and are thought to be the most important for biochemical and subjective restoration. Disturbances of airway tone are uncommon during this stage in normals.

REM sleep is attended by bursts of phasic muscular and ocular activity, and dramatic periodic oscillations of blood pressure, thermoregulation, heart rate, airway smooth muscle tone, and respiratory rate (3). It is generally during REM sleep that the most significant apneas occur in patients with obstructive sleep apnea syndrome (OSA). Although REM periods alternate with non-REM periods every 90 minutes or so, REM sleep is most prevalent during the hours of 0400-0700. It is probably more than a coincidence that this is the period of highest incidence of sudden death, according to a large review of 432,000 deaths (4).

VENTILATION DURING SLEEP IN NORMALS

Following the early studies on "Pickwickian" patients, some quantitative criteria were needed to create useful definitions for clinical decisions and research. A.J. Block et al performed polysomnography on 30 normal men and 19 women (5). Two-thirds of the men exhibited an average of 15 sleep events, defined as apneic periods lasting at least 20 seconds, or episodes of O_2 desaturation of >4%. Interestingly, none of the women experienced any events. Guilleminault's results in a similar study were nearly identical, showing that normal non-obese men, but not (young) women frequently experience sleep apnea. This led to the following definition of terms:

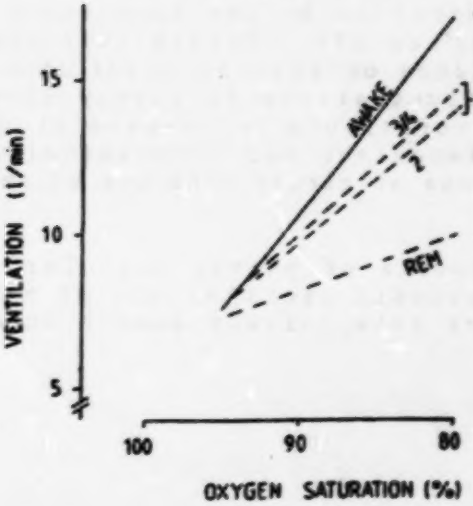
SLEEP APNEA = cessation of air flow at the mouth and nose lasting at least 10 seconds

APNEA INDEX = average number apneic events per hour (NL < 2 per hour)

HYPOPNEA = reduction of air flow at nose and mouth, WITH O_2 desaturation of at least 4% from baseline

SLEEP APNEA SYNDROME = established by observing at least 30 episodes of apnea (not hypopnea) over a 7 hour period, in both NREM and REM sleep (6).

Figure 1



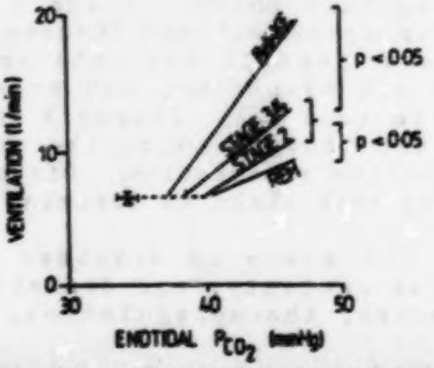


Figure 1. Mean relationships between expired ventilation and increasing end-tidal PCO_2 in 12 subjects, six male and six female, indicating the mean ± SE resting ventilation/CO_2 set point in the awake stage. (Redrawn from Douglas et al.)

CONTROL OF VENTILATION DURING SLEEP

It is now clear that the increase in minute ventilation in response to hypoxia is blunted during sleep in normal adults (see figure 1). This blunting is particularly marked in REM sleep, where in men the hypoxic ventilatory response is only 1/3 that of wakefulness (7). Premenopausal women, however, have no change in hypoxic ventilatory response during NREM sleep; their response during REM sleep is about 1/2 that of wakefulness.

The ventilatory response to hypercarbia is similarly blunted during sleep; again, the effect is greatest during REM sleep, where in men it is only 1/3 that of wakefulness. Women show a similarly depressed response (8), except perhaps during periods of high serum progesterone (9) (see figure 1).

In normal subjects hypoxia appears to be a poor stimulus to arousal, with many subjects remaining asleep with arterial oxygen saturations as low as 70% (10). Although in normals there is no difference in arousal threshold to hypoxia between NREM and REM sleep, in patients with obstructive sleep apnea (OSA), the threshold during REM sleep is even lower (11). Hypercarbia appears to be a more potent arousal stimulus than hypoxia, both in normals and in OSA patients (12). Both additional inspiratory resistance and occlusion of inspiration are potent stimuli to arousal from sleep. Surprisingly, and fortunately, arousal following airway occlusion is far more rapid during REM sleep (13).

Figure 2

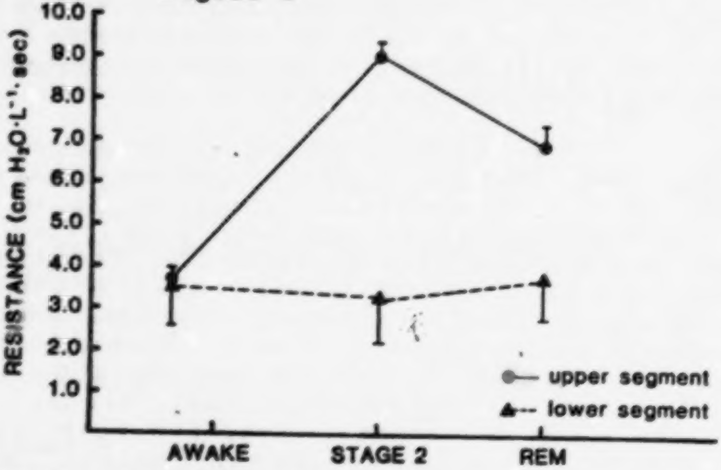


Fig. 2 Inspiratory airflow resistance in healthy adult male subjects during sleep. The resistance in the supralaryngeal airway (solid line) increases significantly while the resistance across the lungs and larynx (dotted line) remains unchanged. (From Hudgel DW, Martin RJ, Johnson B, Hill P: Mechanics of the respiratory system and breathing pattern during sleep in normal humans. J Appl Physiol 56:136, 1984. With permission.)

CONTROL OF UPPER AIRWAY IN SLEEP

Inspiratory airflow resistance during sleep is increased in normal subjects as well as OSA patients (14) (see figure 2). Remmers' early studies established the site of obstruction in most apneas at the pharynx, and focused initial attention on the genioglossus muscle. This muscle, whose function is to pull the tongue forward, was found to be electrically silent during obstructive apneic events (15). This led to an oversimplified view of apnea as airway obstruction by the tongue, due to the combined effects of posture-related gravitational forces, and the primary failure of the normal phasic inspiratory burst of genioglossus activity.

Further clinical studies by Remmers and others (16) elucidated the roles of other pharyngeal muscle groups in maintaining airway patency during sleep, particularly the hyoid group (17). The refined view, then, is as follows: Inspiratory effort creates subatmospheric intraluminal pressures that would, if unopposed, collapse the unsupported upper airway with every breath, whether awake or asleep. This inward narrowing force is counterbalanced by an outward dilating force created by the coordinated activity of the skeletal muscles surrounding the upper airway. The net balance between these two forces will determine airway patency (18).

Normally, during wakefulness and sleep, the net balance of forces favors an open airway. A disruption in this balance, however, causing airway closure, could result from either excessive suppression of upper airway muscle activity, or a disproportionate increase in negative airway pressure. Evidence suggests both these mechanisms are at work in different clinical scenarios.

For example, intranasal occlusion, whether artificially induced in the sleep lab, or naturally occurring as in chronic rhinitis or adenoid hyperplasia, has been shown to markedly increase both obstructive apnea and hypopnea (19,20). Esophageal pressure monitors in these subjects recorded greater than normal negative pressures during nasal occlusion, as minute ventilation had to be supplied by mouth breathing alone; those subjects with the highest negative esophageal pressures had the highest apneic indices and the most profound O_2 desaturation. Alcohol, on the other hand, has been shown to worsen obstructive sleep apnea and even produce obstructive sleep apnea in "normal" snorers, primarily via a reduction in phasic pharyngeal muscle activity.

Recently, it has been suggested that neural activity of pharyngeal muscles in maintaining airway patency may have been overemphasized(21). Contraction of pharyngeal muscles does appear to enlarge the airway, mainly through anterior displacement of the hyoid bone. There is no evidence, however, that this increase in airway SIZE makes the airway any less collapsible -- in other words, we cannot say that the action of these muscles decreases airway compliance. In fact, selective paralysis of pharyngeal muscles in rabbits has no effect on upper airway closing pressure, a measure of airway compliance. Thus obstructive sleep apnea may be due to an underlying abnormality in upper airway compliance, the clinical expression of which is modified by various intrinsic and extrinsic factors, of which muscle activation (and regulation of static airway volume) is just one.

Abnormalities Complicated by Obstructive Sleep Apnea

Anatomical

1. Adenoid and tonsillar hypertrophy in children and adults[17-19]
2. Glottic web and vocal cord paralysis[18]
3. Acromegaly[20,21]
4. Lymphoma or Hodgkin's disease within pharyngeal lymphoid tissue[22]
5. Microagnathia of various causes[17]
6. Ectopic thyroid
7. Upper airway radiation edema or fibrosis[23,24]
8. Mandible retroagnathia (congenital or secondary to trauma), inadequate repair of fractures, or systemic diseases involving the mandible like rheumatoid arthritis[25]
9. Correction of velopharyngeal incompetence in infants[17,26]
10. Severe kyphoscoliosis[27]
11. Cushing's disease or syndrome

Functional

1. Poliomyelitis, muscular dystrophy, amyotrophic lateral sclerosis and other diseases with bulbar incoordination secondary to brain stem abnormalities[28]
2. Acquired dysautonomia[29]
3. Diaphragm pacing for primary alveolar hypoventilation[30]
4. Hypothyroidism
5. Flurazepam induced[31]
6. Alcohol ingestion[32]
7. Testosterone administration[33]
8. Eplipesy[34]
9. Encephalitis[35]

Figure 3

CLINICAL FEATURES OF OBSTRUCTIVE SLEEP APNEA

The true incidence of obstructive sleep apnea is unknown, but it appears to be primarily a disorder of males and post-menopausal women. The incidence and severity does seem to be positively correlated with extent of obesity; however, in a study of very obese, rather young men and women about to undergo gastric bypass surgery, only the men had sleep-disordered breathing. In fact, the only man who did NOT have obstructive sleep apnea in the study suffered from longstanding hypogonadism (22). Although the mechanism is unclear, it appears that the respiratory stimulant effect of progesterone in pre-menopausal females "protects" them from sleep-disordered breathing.

Obstructive sleep apnea is an underdiagnosed disease, probably because the cardinal symptoms, snoring and excessive daytime sleepiness, are not part of the standard review of systems. In addition, the patient, even if aware of the symptoms, often feels embarrassed to mention them because of their cherished status in the comic repertoire of our popular culture.

SNORING

Snoring is the sound generated by vibration of the soft tissues at an area of stenosis, or collapse. It is the mechanical dissipation of inspiratory muscle pressure, and cannot be equated with upper airway closure, although it is a marker for it. All obstructive sleep apnea patients who have not had pharyngeal surgery snore, and most of them began before age 21. Certainly "normal" people snore as well -- up to 85% of married men in one study (23). There appears to be a continuous spectrum from intermittent light snoring, habitual heavy snoring, and frank obstructive sleep apnea syndrome; one's place in this continuum is not fixed. For example, excessive weight gain, alcohol ingestion, or use of sleeping pills could cause an asymptomatic habitual snorer to develop symptomatic obstructive sleep apnea, or cause an occasional light snorer to snore heavily.

A careful snoring history, then, is important in raising clinical suspicion for obstructive sleep apnea. Four or five loud snores followed by silence, then another series of loud snores is a sure description of a subject with obstructive sleep apnea. In contrast, a history of rhythmic snoring, interspersed with episodes of crescendo-descrescendo snoring, indicates predominantly heavy snoring with few episodes of obstructive apnea. Of course, this history can only be obtained from the bed partner, whose history may be out-dated, since many partners of heavy snorers have long since moved into separate bedrooms by the time of the clinical evaluation.

Clinical Assessment of Daytime Sleepiness

DEGREE OF SLEEPINESS	SEVERITY OF APNEA
1. *Extreme sleepiness*	*Marked sleep fragmentation—severe sleep hypoxemia*
Falls asleep during motor activity, e.g., talking, eating Falls asleep during clinical history taking and physical examination Incapacitated by sleepiness (no longer works, cannot drive motor vehicle)	Typically repetitive obstructive apnea Usually severe hypoxemia during every apnea (SaO_2 80%) Profound hypoxemia in REM sleep (SaO_2 60%)
2. *Unequivocal Sleepiness*	*Marked sleep fragmentation—wide range of hypoxemia*
Falls asleep at rest, e.g., reading, watching TV Falls asleep while driving Can keep awake with physical activity Severely affects daytime functioning Patient typically aware of problem	Repetitive apnea Variable degree of hypoxemia (some have marked desaturation—REM sleep) Some have repetitive short apnea minor desaturation
3. *Mild Sleepiness*	*Variable sleep fragmentation—mild hypoxemia*
Extension of normal diurnal sleepiness Typically denied by patient Asleep while reading, watching TV More marked when "overtired" Persists despite long night sleep Does not apparently interfere with work to any major extent	Episodic apnea, stage 1–2 NREM and REM sleep Apnea occurs in "runs" over 15–20 minutes Preservation of stage 3–4 NREM sleep Mild hypoxemia

EXCESSIVE DAYTIME SLEEPINESS

This important symptom is summarized in the accompanying table (24). The typical obstructive sleep apnea patient suffers 300-500 apneic events each night; in fact he may spend more than half his sleep time not breathing. Each of these events is terminated by an arousal response; as a result very little restorative Stage 4, "slow-wave" sleep is achieved. This causes excessive daytime sleepiness, the severity of which is useful to separate into the three clinical classes delineated in the table from Sullivan's article. Since this triage correlates well with apnea severity, the clinician can estimate the urgency for polysomnography in different patients.

OTHER SYMPTOMS

Patients also exhibit abnormal motor behavior during arousal at termination of an apneic event, and may thrash about, striking and even injuring their wives (still another reason for separate rooms). They may be impotent, thought to be due to acquired pituitary hypofunction (25). Morning headaches are common, probably due to increased cerebral blood flow from prolonged hypoxia. Severe cases will show varying degrees of intellectual deterioration, nocturnal enuresis, and nocturnal seizures. The result is often severe marital stress, job difficulties, and secondary depression.

PHYSICAL EXAM

Obesity is a common finding, as discussed previously. Although by no means universal, a characteristic finding is a short, thick neck, with redundant vertical folds in the tissues of the posterior pharynx. Retrognathia, causing hypopharyngeal stenosis, tonsillar and adenoidal hypertrophy, and the macroglossia of hypothyroidism should be looked for carefully. Systemic hypertension, initially a transient epiphenomenon from the increased cardiac output in response to hypoxia, becomes fixed in 50% (26). Ankle edema heralds the development of right-heart failure from pulmonary hypertension, though of course many obese individuals have "benign" ankle edema.

LABORATORY FINDINGS

There are no laboratory tests that can be performed during wakefulness that will specifically predict whether sleep apnea will be found in a given patient. If the pharyngeal airway is narrow in the sitting position, maximal expiratory and inspiratory flow rates may be decreased, and the flow-volume loop will be consistent with extrathoracic airflow obstruction (see figure 5). In addition to flow restriction, "sawtoothing" may be seen on the forced inspiratory flow-volume loop. This pattern, frequently seen in obstructive sleep apnea patients, correlates with heavy snoring and is thought to be caused by vibrations of redundant pharyngeal tissue (27).

Erythrocytosis may be seen, especially in patients who are also mildly hypoxic during the day. Thyroid function tests should probably be measured in every patient being evaluated for obstructrive sleep apnea; hypothyroidism is an easiy correctible cause of obstructive sleep apnea. If acromegaly, another endocrine cause of obstructive sleep apnea, is suspected growth hormone measurements can be made.

The awake arterial blood gas is also quite useful. Patients (e.g. with COPD) with resting waking hypoxia live on the "steep part" of the oxygen-hemoglobin dissociation curve; even mild apnea in these patients, with only small drops in pO_2, can cause linear, life-threatening drops in SaO_2. In addition, some patients with sleep apnea will experience alveolar hypoventilation during wakefulness, with resultant hypercarbia. This may be due to depressed ventilatory drive mechanisms, increased mechanical load to breathing from obesity, or weak respiratory muscles. (This is discussed more fully in a later section).

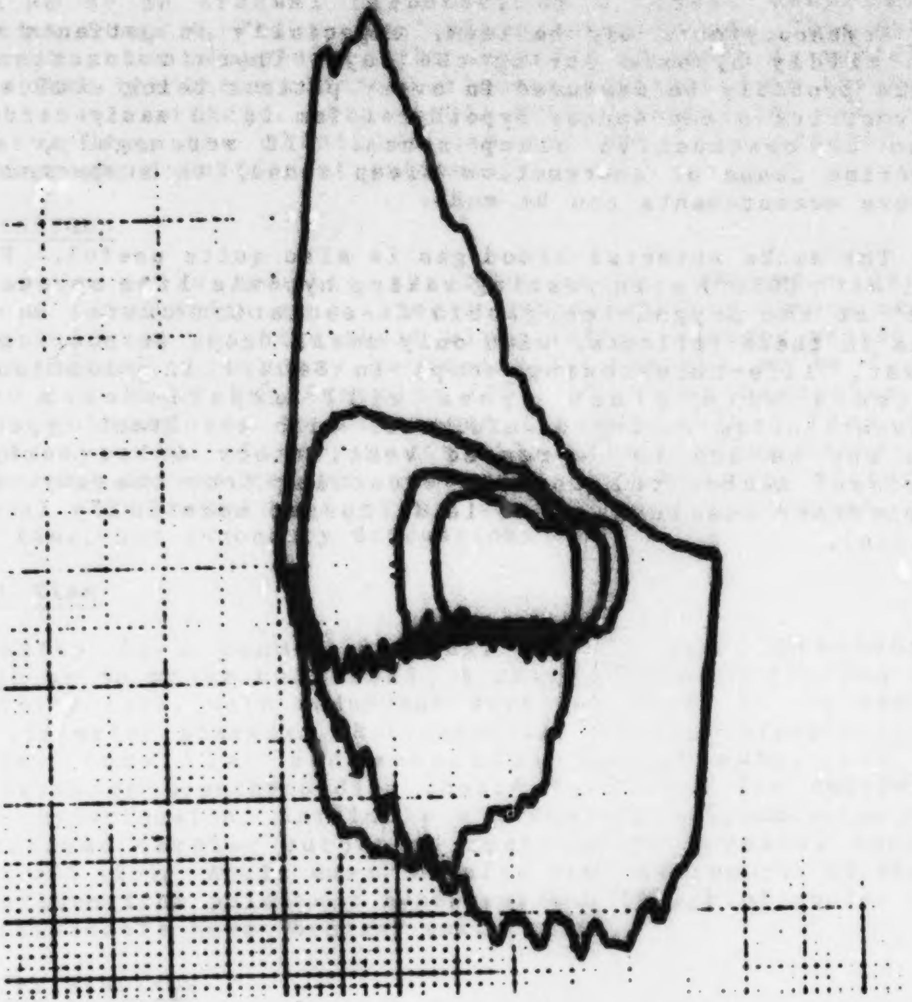


Figure 5 This demonstrates the "saw-tooth" pattern that is typically seen on flow-volume loops in patients with obstructive sleep apnea. Flow is vertical, volume is horizontal, inspiration is upward and expiration downward. The "sawtooth" pattern is seen on the inspiratory loops of both tidal breathing and breath to total lung capacity. This type of pattern may be seen only on inspiration, expiration or during both phases of the respiratory cycle.

POLYSOMNOGRAPHY

A full sleep study is the only definitive way to establish a diagnosis, assess disease severity, and determine the urgency for treatment. True, in many cases apnea can be demonstrated soon after sleep onset in "nap" studies. All night monitoring, however, is necessary to examine the apnea characteristics during REM sleep, which usually is most prevalent around 4 to 6 a.m. It is during this period that the most profound oxygen desaturations and dysrhythmias occur (55).

At a bare minimum polysomnography should be able to record oronasal airflow (thermistors, or pressure transducers), respiratory effort (surface inductive plethysmography (SIP) via Respitrace), continuous determinations of O_2 saturation, ECG monitoring, and EEG data for sleep staging. Diagnosis is established by observing paradoxic movement of the rib cage and abdomen with O_2 desaturation. Two measurements guide urgency for treatment: the extent of O_2 desaturation and the pattern of dysrhythmias.

The mechanisms that trigger the airways to open and terminate an apneic event are unknown, but recent studies (40) suggest that the airways may be triggered to open by a protective reflex originating in the larynx or in the inspiratory muscles upon reaching a certain tension-time index (degree of contraction). Neural information from the fatiguing muscles is fed back to the respiratory centers, which then modulate output to the pharyngeal muscles so that the obstruction is relieved and the respiratory muscles are unloaded.

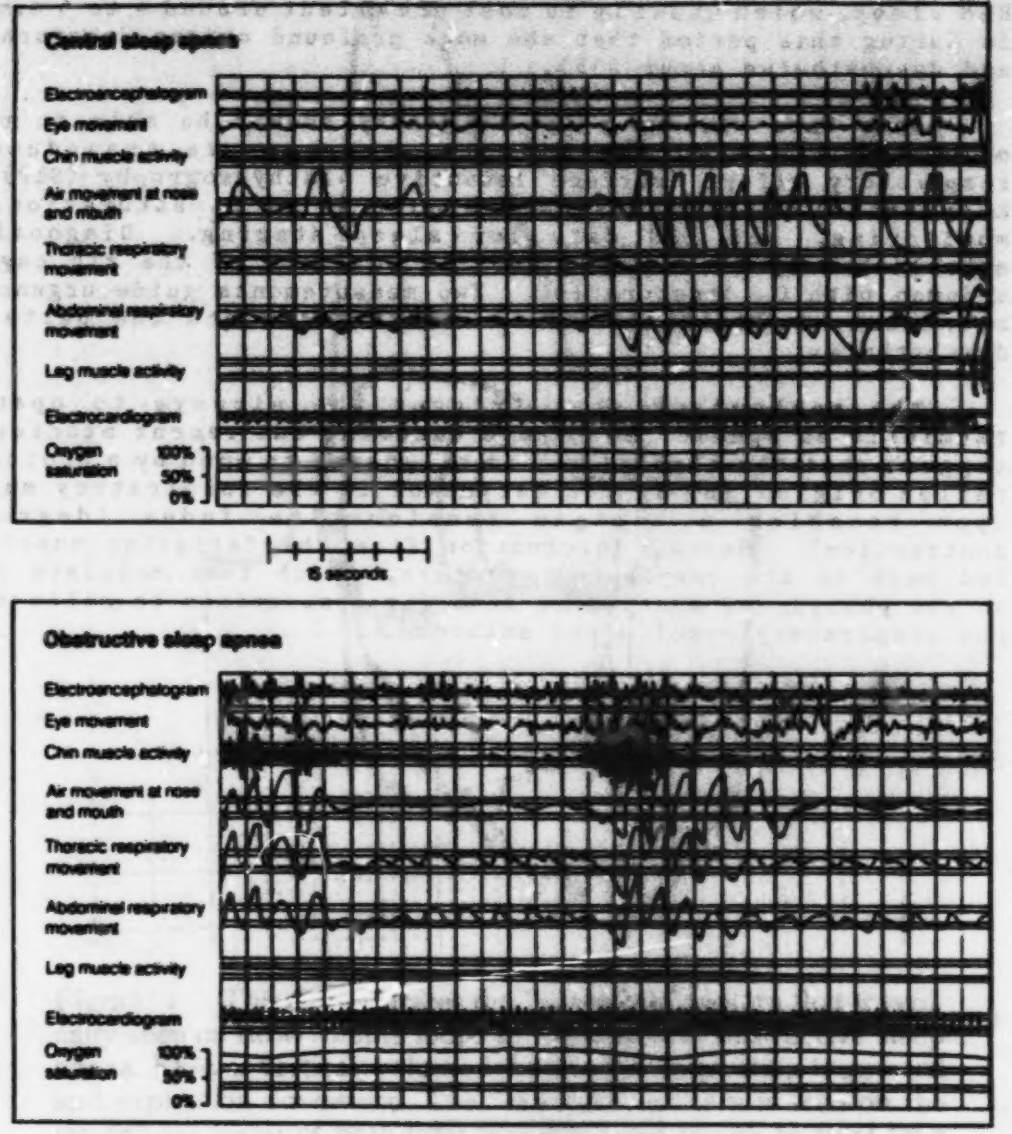


FIG. 6 Polysomnographic tracings contrast central vs. obstructive sleep apnea. Note more pronounced thoracic and abdominal respiratory movements in obstructive sleep apnea patient (bottom) as well as decreases in oxygen saturation. (From ref. 15.)

HEMODYNAMIC AND DYSRHYTHMIC EFFECTS IN OBSTRUCTIVE SLEEP APNEA

It is now apparent that obstructive sleep apnea patients become hypoxic through mechanisms other than simply hypoventilation, in that the A-a gradient widens (28). Higher closing pressures have been documented in some patients, which could produce extensive shunting. Repeated desaturations produce pulmonary hypertension.

Most studies show that PA pressures increase progressively through the various sleep stages in obstructive sleep apnea, reaching about twice baseline in REM sleep (29,30). In estimating the acute effects of this rise on right ventricular function, one must recall that right ventricular afterload is determined by subtracting pleural pressure from pulmonary artery pressure. It is this value (Ppa - Ppl) that represents the actual transmural pressure gradient against which the right ventricle must work. Eventually, the pulmonary artery pressure elevation becomes sustained over a 24-hour period; it is these patients who develop chronic cor pulmonale. It has been pointed out, however, that patients with clinically evident right-heart failure have more chronic airflow obstruction, diurnal hypoxemia, and hypercarbia than those without right heart failure. Thus, concomitant COPD may be a more important determinant of right heart failure than the sleep apnea per se.

Guilleminault has studied cyclic variation in heart rate in obstructive sleep apnea patients (31). At onset of apnea all 400 patients showed progressive bradycardia, followed by abrupt tachycardia upon resumption of breathing. This pattern was not seen in controls without sleep apnea, raising the possibility that this pattern on a 24-hour Holter could be used as a screening tool. Atropine blocked the pattern, while 100% O_2 had no effect; indicating that these ECG changes are mediated by the autonomic nervous system. Further studies by the same author showed that cardiac index also falls during apneic periods (32), thus implying that ventricular dysrhythmias during this period would be particularly dangerous.

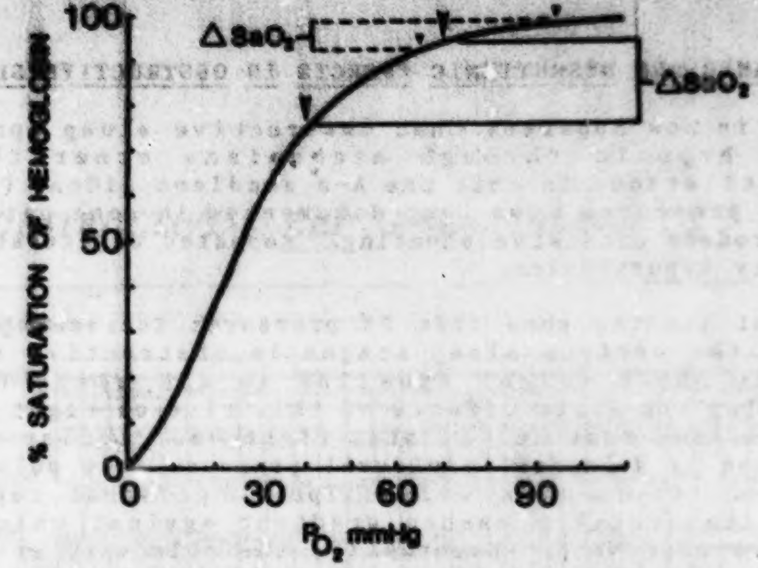


Fig. 7 Affect of initial PO_2 on amount of arterial oxygen desaturation seen. Because of the shape of the oxygen-hemoglobin dissociation curve, the amount of decrease in SaO_2 seen with equivalent decrease in PO_2 is different for different starting PO_2's. When the starting PO_2 is near or below the "elbow" of the curve more desaturation is seen.

Figure 7

Arterial Blood Gas Fluctuations During Sleep in Obstructive Sleep Apnea

	Awake	Sleep Nonapneic	Apneic Period
pH	7.43	7.42	7.36
PCO_2 (mm Hg)	35	36	44
PO_2 (mm Hg)	56*	50	31
O_2 Saturation (percent)	92	89	67
CO_2 Content (mMol/L)	23	24	25

* Measurement made in asthmatic patient in Denver, Colorado—normal PO_2 = 69 ± 10 (2SD) mm Hg.

Figure 8

The incidence of complex ventricular dysrhythmia in obstructive sleep apnea varies directly with the extent of O_2 desaturation, becoming frequent at O_2 saturations below 70% (33).

Cardiac Arrhythmias during Sleep in Patients with Sleep Apnea

	MILLER	GUILLEMINAULT ET AL.	SHEPARD ET AL.
Patients (no.)	23	400	31
Sinus bradycardia (< 30 beats per min)	9%	7%	10%
Sinus pauses (2 to 13 seconds)	9%	11%	10%
Second-degree atrioventricular block	4%	8%	6%
Ventricular ectopy			
Any	57%	—	74%
Complex	9%	—	55%
Ventricular tachycardia	0%	3%	3%

Figure 9

CLINICAL VARIANTS OF SLEEP APNEA AND RELATED DISORDERS

HEAVY SNORING WITH EPISODIC APNEA

These are patients in transition from heavy snoring to sleep apnea, who begin to develop a few episodes of complete obstructive apnea against a background of partial obstructions. Hypopneas and crescendo-descrescendo snoring are frequent in stages 1 & 2, often with minor falls in SaO_2. In stage 4 NREM sleep breathing stabilizes, and the patient usually snores with a steady SaO_2. During REM sleep, hypopnea returns, and a few episodes of complete obstruction lead to arousals, often to wakefulness. It is this patient with mild disease who complains of nocturnal "choking" episodes, which are often misinterpreted as paroxysmal nocturnal dyspnea. As apneas become more frequent, sleep deprivation and thus the need for sleep increase, so the arousals no longer reach alert consciousness, and the patient no longer complains of this symptom.

MILD OBSTRUCTIVE SLEEP APNEA/REM APNEA

This is a very common form of the disease, in which frequent obstructive apneas are seen in the early sleep stages, with only heavy snoring in stage 4 NREM sleep. During REM sleep, however, repetitive complete obstructive sleep apnea causes significant O_2 desaturations. Often, the apnea in these patients can be abolished by sleep in the upright position. Daytime somnolence is not severe, presumably because stage 4 NREM sleep is preserved. These patients are only mildly overweight, and present with vague personality changes and loss of mental acuity (33). Weight loss in this group is frequently curative.

DAYTIME AWAKE CO_2 RETENTION

Most patients with obstructive sleep apnea have a normal pCO_2. A subgroup have daytime pCO_2 >45, usually with resting pO_2 <70. These patients, almost always very obese, have been termed "Pickwickian", though many patients with the obesity hypoventilation syndrome do not have sleep apnea. Sleep apnea itself does not cause daytime CO_2 retention; many of these patients have been shown to have obstructive airway disease (34). Others have a defect in the "front-line" defense against obstructive sleep apnea, the carotid body chemoreceptors. Both ventilatory and arousal responses to airway occlusion are mediated through the carotid bodies; the central chemoreceptors play a back-up role (35). The delay in response to occlusive apnea results in a greater dose of hypoxia. Further depression of the arousal response may be related to an excessive alcohol intake in this group (36). As a result of this depressed arousal response, these patients often do not have much day time sleepiness, despite sleep studies showing long periods of hypoventilation, precipitous falls in SaO_2 in both NREM and REM sleep, CO_2 retention, and even nocturnal seizure activity.

Only about half the patients with the obesity-hypoventilation syndrome will show clinical and hemodynamic improvement with treatment of their obstructive sleep apnea. The group that improved showed an unfavorable balance between ventilation during time awake -- which was normal -- and hypoventilation during periods containing apnea. This group simply cannot catch up; treatment of their obstructive sleep apnea cures their CO_2 retention as well as their obstructive sleep apnea-related hemodynamic abnormalities. The non-responders demonstrated sustained hypoventilation even while awake; although treatment of their obstructive sleep apnea may well be indicated, it has no effect on the hypercarbia -- these are the "true" Pickwickian patients (37).

CENTRAL AND MIXED APNEA (ONDINE'S CURSE)

Central apneas are periods of absent airflow associated with absence of diaphragmatic efforts. Mixed apneas comprise a period of central apnea followed by some occlusive apneas. Central apnea is thought to result from loss of inhibitory inputs to brainstem reflexes that inhibit breathing when upper airway closure occurs. This is usually the result of forebrain damage, but can also occur in patients with severe unrelated congestive heart failure. For reasons not entirely clear, this condition also responds to nasal CPAP, though the required dose is higher (56).

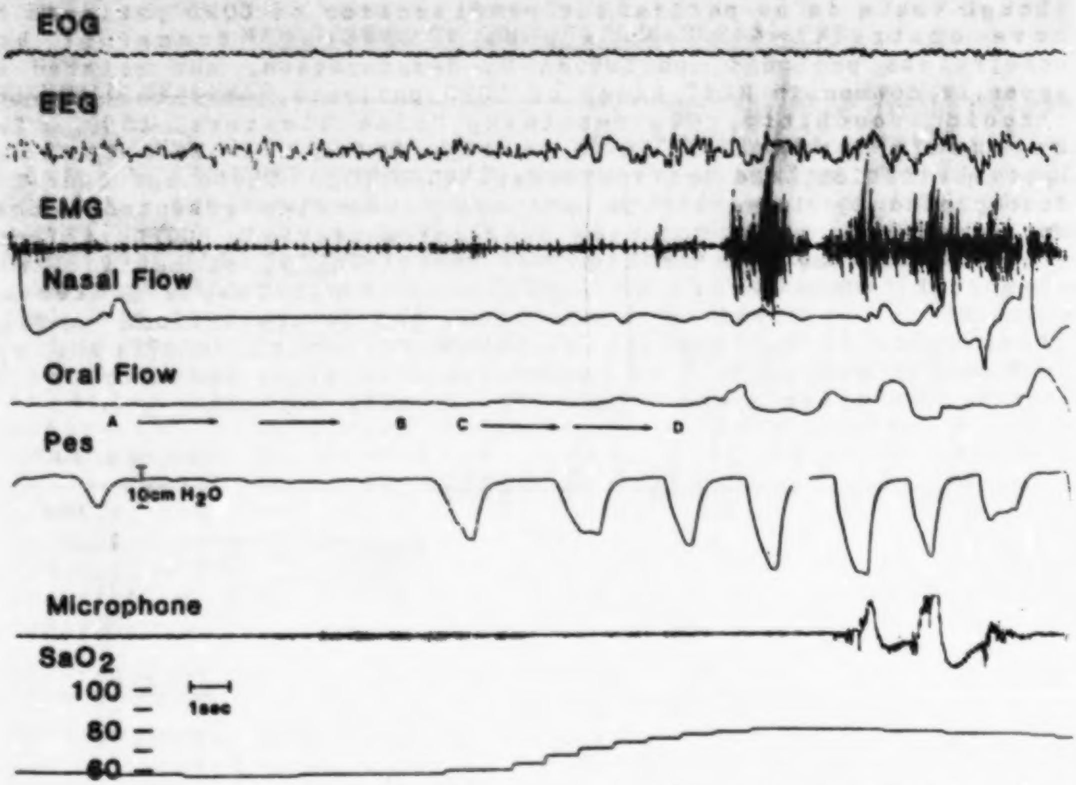


Fig. 10 Mixed apnea. An eight second central apnea (A → B), as evidenced by lack of inspiratory efforts in the chin EMG and esophageal pressure tracings, precedes a typical obstructive event (C → D).

Figure 10

NARCOLEPSY

This distinct clinical syndrome consists of irresistible daytime hypersomuolence, usually in association with cataplexy (sudden loss of skeletal muscle tone in response to strong emotions), sleep paralysis, or hypnogogic hallucinations (vivid, life-like dreams at sleep onset). Narcolepsy is diagnosed by recording, at least 2 of 4 times, REM sleep within 15 minutes of sleep onset during daytime monitoring. Approximately 6% of narcoleptics have the sleep apnea syndrome (57).

SLEEP IN COPD

COPD and obstructive sleep apnea can obviously coexist, though there is no particular predilection of COPD patients to have obstructive sleep apneas. However, transient but nonetheless profound nocturnal O_2 desaturation, not related to apnea,is common in REM sleep of COPD patients, particularly the chronic bronchitic, CO_2-retaining "blue bloaters" (50). The hypoxemia arises from a combination of REM-induced hypoventilation, and intrapulmonary shunting. These episodes are accompanied by increases in pulmonary vascular resistance that are reversible with nocturnal O_2 supplementation. COPD patients who have daytime hypoxia are, not surprisingly, at particularly high risk; they should be screened with continuous nocturnal oximetry, or at least by supine blood gas determination. A full sleep study is unnecessarily expensive, unless the "overlap" syndrome is suspected from the presence of signs and symptoms of obstructive sleep apnea -- snoring, morning headache, etc.

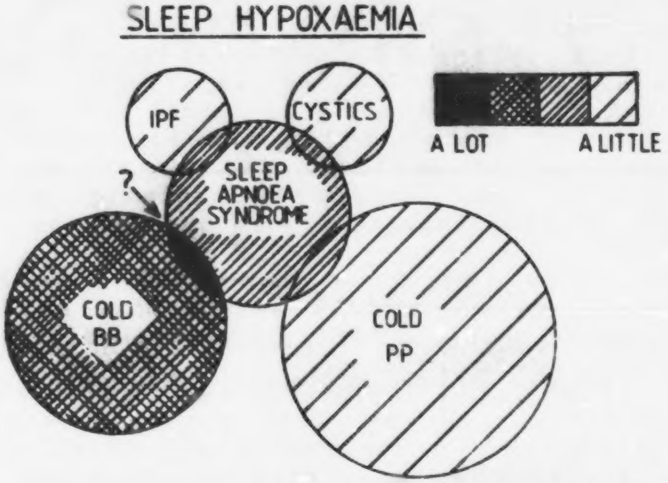


Figure 11 Possible incidence of the "overlap syndrome" in a population, as shown on a Venn diagram. Some patients have the "pink and puffing" pattern of COPD, with minor hypoxemia during sleep, and some have the "blue and bloated" pattern with more profound hypoxemia in sleep, notably during REM periods, but whereas hypoxemia in sleep is also common in the obstructive sleep apnea syndrome, the overlap between obstructive sleep apnea and chronic obstructive lung disease with the "blue and bloated" pattern yields the overlap syndrome, with relatively profound nocturnal hypoxemia. Nocturnal hypoxemia also occurs in some patients with cystic fibrosis and idiopathic pulmonary fibrosis, and it seems possible that an overlap with obstructive sleep apnea coincidentally may also occur in some of these patients.

Figure 11

MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA

GENERAL MEASURES

Weight loss is advisable for obstructive sleep apnea patients, but the clinical response is quite unpredictable (38,39). Avoidance of alcohol and sedatives, especially in the three hours before retiring, is important. Patients with rhinitis will often show improvement in apnea index after treatment with decongestants. Supplemental nocturnal O_2 improves SaO_2 and improves sleep rhythm in NREM sleep, (38) but has no effect on apneic events during REM sleep -- when the dangerous episodes occur. Correction of hypothyroidism, though eventually curative for associated obstructive sleep apnea, must be undertaken with care. Often a hypothyroid patient's low O_2 consumption is protective against hypoxic catastrophe; replacement therefore should be slow, and another means of treating the sleep apnea should be employed at least temporarily. Nasopharyngeal airways, whose tip extends into the hypopharynx, and tongue restraining devices are quite effective at preventing obstructive sleep apnea, but suffer from poor patient acceptance (58).

DRUG THERAPY

Despite tantalizing epidemiologic observations that premenopausal women exhibit neither sleep apnea nor a markedly blunted hypercarbic ventilatory response, progesterone has no effect on apneic index in obstructive sleep apnea patients. However, it does increase ventilatory drive in men with the obesity-hypoventilation syndrome, improving blood gases, lowering mean pulmonary artery pressure, and relieving cor pulmonale (39). The main side effect is impotence, seen in 20%.

Protriptyline, a tricyclic antidepressant, reduces time spent in REM sleep. Although it improves the average nocturnal SaO_2 and daytime somnolence in some patients (40), it has no effect on apnea index, and is not well tolerated in patients with severe obstructive sleep apnea because of its anticholinergic side effects. It may have a role in patients with mild, predominantly REM-related obstructive sleep apnea.

Strychnine, a lycine antagonist, in low doses can reduce obstructive sleep apnea. The drug does increase resting pharyngeal tone (?reducing compliance), but also increases glossal sensitivity to hypoxia (41).

SURGICAL TREATMENT

The upper airway is divided into the naso-, oro-, and hypopharynx. The first two are separated by the soft palate, and the latter two by the tip of the epiglottis. Obstruction in any of these three areas can and does produce obstructive sleep apnea. During physical examination a surgically correctible cause of obstructive sleep apnea may be identified, such as septal deviation, adenoid hypertrophy, nasal polyps, craniofacial abnormalities (as in the Treacher-Collins or Pierre-Robin syndromes), or retrognathia. Although appropriate surgery in these cases can cure obstructive sleep apnea with all its attendant morbidity, these patients are a minority.

Most obstructive sleep apnea patients do not have an easily identifiable anatomic defect. For these patients, until recently, tracheostomy was the only definitive cure. Several studies showed that hemodynamic abnormalities rapidly improved post-op, and daytime hypersomnolence disappeared within 1-2 months (42). The procedure is disfiguring, however, and for other than the most life-threatening apnea is not usually indicated. However, the obstructive sleep apnea patient who is morbidly obese often does not respond (or responds incompletely) to lesser surgery. There is strong evidence to suggest that this sub-group, which often has COPD as well (overlap syndrome), will not experience reversal of pulmonary hypertension and cor pulmonale unless the apnea is COMPLETELY cured (52). These patients should, therefore, be treated with tracheostomy "up front" (60).

CEPHALOMETRICS

Every patient being considered for surgical correction of obstructive sleep apnea should have a radiographic attempt to identify the site of occlusion. Hudgel has noted that the site of upper airway obstruction varies among obstructive sleep apnea patients, and is not predictable from pressure gradients measured during wakefulness. Lateral somnofluoroscopy has been used to detect the site of obstruction, and in one study (43) the results could be used to predict clinical response to UPPP. More prevalent is the use of cephalometrics, a technique previously used for analysis of facial growth and skeletal deformities. (PLEASE SEE FIGURES FOR EXPLANATION) In a study of UPPP failures, a small posterior air space of 4-5mm (nl=11-13mm) was the only consistent cephalometric finding, indicating hypopharyngeal obstruction (44).

Cephalometrics. This technique was previously used for analysis of facial growth and development and dental and skeletal abnormalities (Fig. 6-5). The modified measurements felt to be important in apneics[78] appear in Figure 6-4. Angle SNA (maxilla) and SNB (mandible)—should be 82 ± 2 degrees and 80 ± 2 degrees, respectively. Lesser angles indicate maxillary or mandibular deficiencies that may be contributing to apnea. PAS (posterior airway space)—in normals is 11 ± 1 mm. Apneics with a 3–4 mm PAS may not benefit from UPPP alone since the obstruction is behind the tongue. PNS-Pg (soft palate)—in normals is 37 ± 3 mm (PNS-Pg). A longer soft palate may indicate that UPPP would be helpful (Fig. 6-6). MPH (hyoid position)—in normals is 15.4 ± 3 mm below a perpendicular along the inferior border of the mandible. A low hyoid usually accompanies a small PAS and implies poor results from UPPP alone.[79]

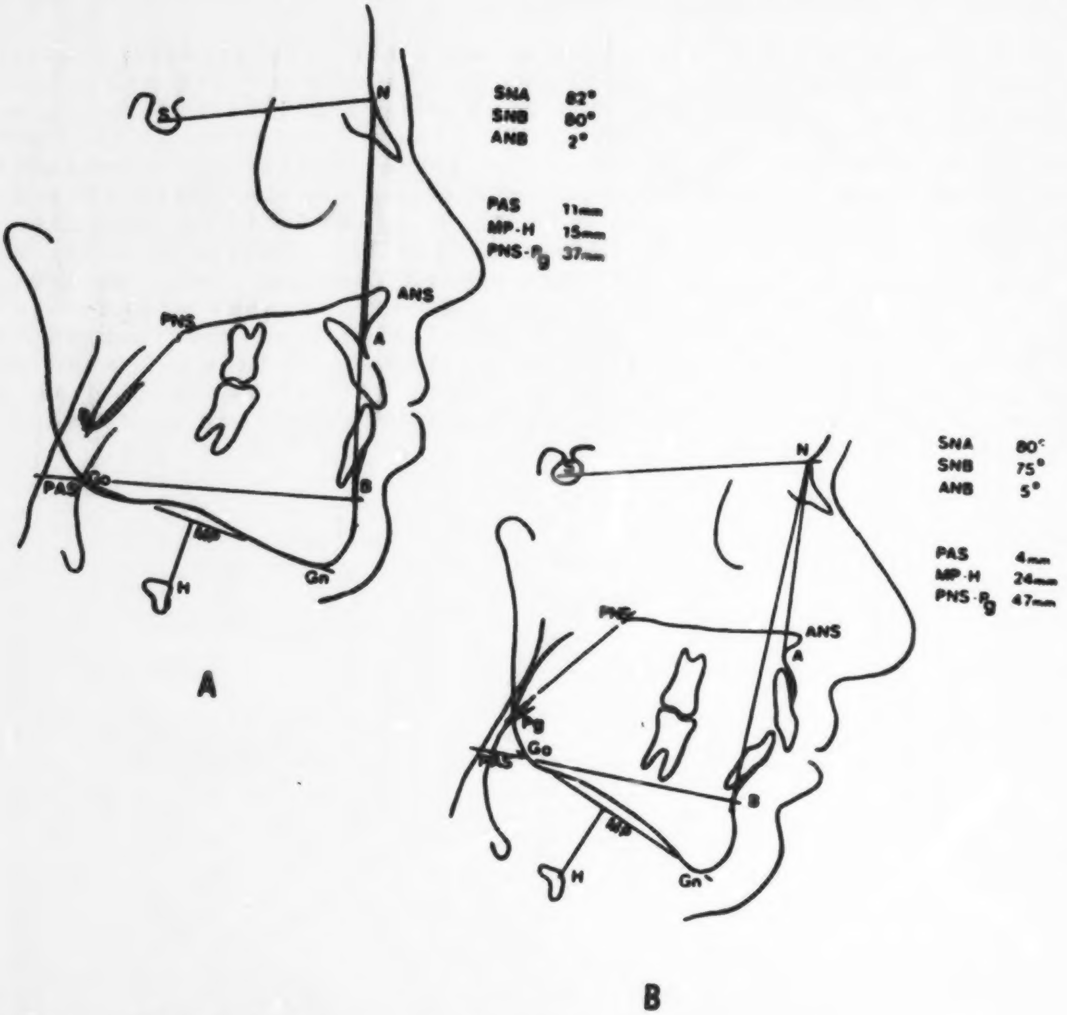

S
N
SNA 82°
SNB 80°
ANB 2°
PAS 11mm
MP-H 15mm
PNS-Pg 37mm
ANS
PNS
A
Go
PAS
B
MP
Gn
H
A
S
N
SNA 80°
SNB 75°
ANB 5°
PAS 4mm
MP-H 24mm
PNS-Pg 47mm
PNS
ANS
A
Pg
Go
PAS
B
MP
Gn
H
B

Fig. 12 Diagramatic representation of cephalometric measurements in normal subject (A) and one with slight retroagnathia (B). Note the narrow posterior airspace (PAS) and long soft palate (PNS-Pg) in example B. See text for explanation and normal values. (From Riley R, et al: Sleep 6(4):303–11, 1983. With permission.)

In addition to cephalometrics, Fujita recommends fiberoptic nasopharyngolaryngoscopy, using a Müller maneuver to obtain a dynamic view of the site of obstruction. Using these techniques, Fujita has classified patients with obstructive sleep apnea syndrome into three types: Type I patients have airway narrowing primarily in the oropharynx; the palatal arch is in normal position. These patients characteristically have large tonsils, enlarged uvulae, and redundant pillar mucosa.

Type II patients have low palatal arches and big tongues. The IIa subgroup has only oropharyngeal obstruction; the IIb's have BOTH oropharyngeal and hypopharyngeal obstruction, whether from retrognathia, hypertrophied lingual tonsils, or redundant aryepiglottic folds (45).

UVULOPALATOPHARYNGOPLASTY (UPPP)

Fujita developed surgery to enlarge the oropharyngeal lumen, originally to cure snoring. It consists of excising redundant oropharyngeal tissues from the free margin of the soft palate, tonsillar pillars, and uvula. After excision, the non-collapsible oropharyngeal space is reconstructed by stretching the posterolateral wall and approximating the two palatal arch muscles. Because this surgery is very effective in curing snoring (inspiratory muscle pressure from the occlusive event no longer is dissipated into the pharyngeal tissues), most patients report subjective improvement; their bed-partners return, at least. However, in series unselected for site of obstruction by cephalometrics or fiberpharyngoscopy, only half will show at least 50% improvement in apnea index (46). If only Type I patients are submitted to UPPP, the rate of objective improvement reaches 70-90% (47,48).

Uvulopalatopharyngoplasty—A Review of Results

Reference	Number of Subjects	Multiple Sleep Latency Test (min) Pre-Op	Multiple Sleep Latency Test (min) Post-Op	Subjective Improvement N	Subjective Improvement (%)	Apnea/Hypopnea Index Pre-Op	Apnea/Hypopnea Index Post-Op	Over 50% Reduction in Apnea/Hypopnea Index Number	Over 50% Reduction in Apnea/Hypopnea Index (% of Total)
Fujita[41]	12	—	—	11	(92%)	54.0	27.7	8	75%
Hernandez[42]	10	—	—	10	(100%)	—	—	—	—
Simmons[43]	18	—	—	15	(83%)	45.4	28.7	9	45%
Silvestri[46]	14*	3.7‡	5.3	14	(100%)	45.9	36.1	7	50%
Zorick[47]	31	3.9	6.6	—	—	61.9	29.9	16	52%
	(16 responders)	(3.4)	(9.6)	—	(94%)	(64.4)	(11.7)	—	—
	(15 nonresponders)	(4.4)	(3.7)	—	(58%)	(59.2)	(49.4)	—	—
Walsh[48]	11	—	—	5	(45%)	73.8	58.7	—	—
Cohn[49]	92	—	—	72	(81%)	65.8§	34.4	—	—
Smith[50]	7	3	4	7	(100%)	64.0	25.0	—	—
Guilleminault[51]	35†	—	—	31	(89%)	—	—	27	69%‖
Fujita[52]	66	—	—	—	—	—	—	33	50%
	(33 responders)	—	—	—	—	58.3	9.5	—	—
	(33 nonresponders)	—	—	—	—	60.2	55.4	—	—
Schoen[53]	13	—	—	—	—	58	22	10	77%
Thorpy[54]	15	—	—	15	(100%)	92	27	—	—
Santamaria[55]	24	—	—	—	—	34	13	15	63%
Askenasy[56]	10	—	—	—	—	—	—	4	40%
Norman[57]	43	—	—	—	—	52.5	40.5	19	44%
Scrima[58]	15	—	—	—	—	43.7	18.4	9	60%
Total	416	—	—	180	(85%)	57.8	30.5	157	56.8%

* = Heavy snorers with only hypopneas excluded.
† = Severe patients requiring tracheostomy excluded.
‡ = 5 patients.
§ = 19 patients.
‖ = Estimated from data.

HYPOPHARYNGEAL SURGERY

Hypopharyngeal surgery is indicated as the second stage procedure following UPPP in type IIb patients, or as the primary procedure in Type III patients. There are three approaches. The first is to reduce the bulk of collapsible hypopharyngeal mucosa, such as is present on occasion in and around the aryepiglottic folds. The second is mandibular advancement, employed to correct retrognathia, to protrude the mandible and enlarge the hypopharyngeal space. A promising new technique is hyoid osteotomy, where the hyoid is widened, thus increasing the diameter of the hypopharynx. This procedure makes the most sense teleologically, since the hyoid and its muscles are the most important determinant of hypopharyngeal volume. In addition, hyoid osteotomy is less invasive than the other techniques (49).

NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE (NASAL CPAP)

First described in 1981, nasal CPAP prevents oropharyngeal closure by providing a continuous background of positive pressure, so that the collapsing inspiratory pressure never falls below atmospheric. It is a sort of "pressure splint" (53); upper airway compliance is decreased. The surgical procedures described above, on the other hand, are designed primarily to increase cross-sectional area of the upper airway at various points -- the decrease in airway compliance they afford through "tightening" of mucosal surfaces is secondary. One might speculate that the degree to which surgery such as UPPP is successful is due to the degree that it emulates nasal CPAP in stiffening the airway.

Normal subjects will experience airleak with nasal CPAP. When the device is applied to obstructive sleep apnea patients, however, the tongue and soft palate are pushed together away from the posterior pharynx, creating a hermetic seal.

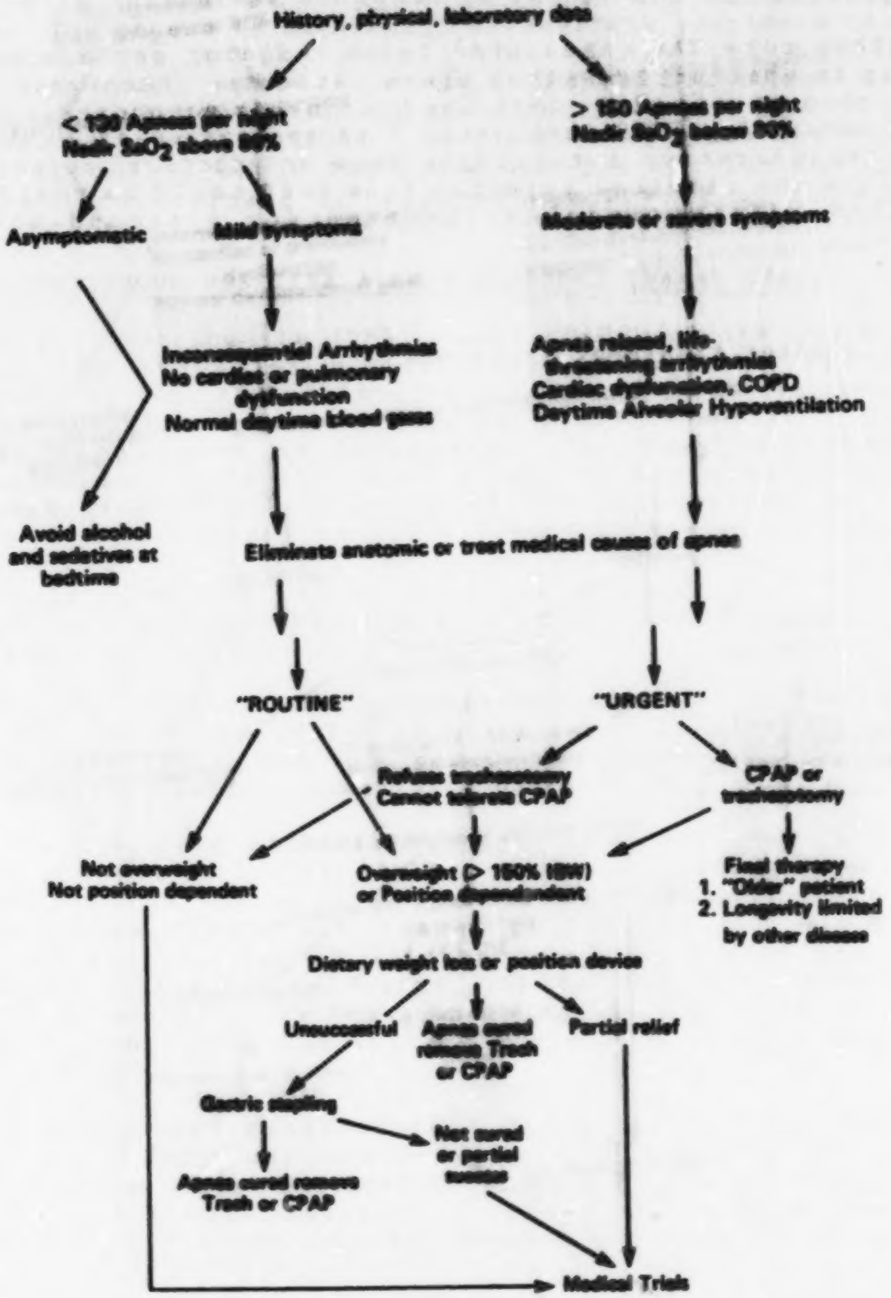
The immediate clinical response to nasal CPAP is dramatic. Within moments of its application, occlusive events cease, and the patient enters a period of long, "rebound" stage 4 NREM sleep. Also, there are longer periods of REM sleep. This rebound period, during which arousal responses are markedly depressed, lasts for 7-10 days, after which sleep architecture returns to normal. Daytime somnolence and cognitive defects are usually eliminated, and patient compliance is high (54), about 80%.

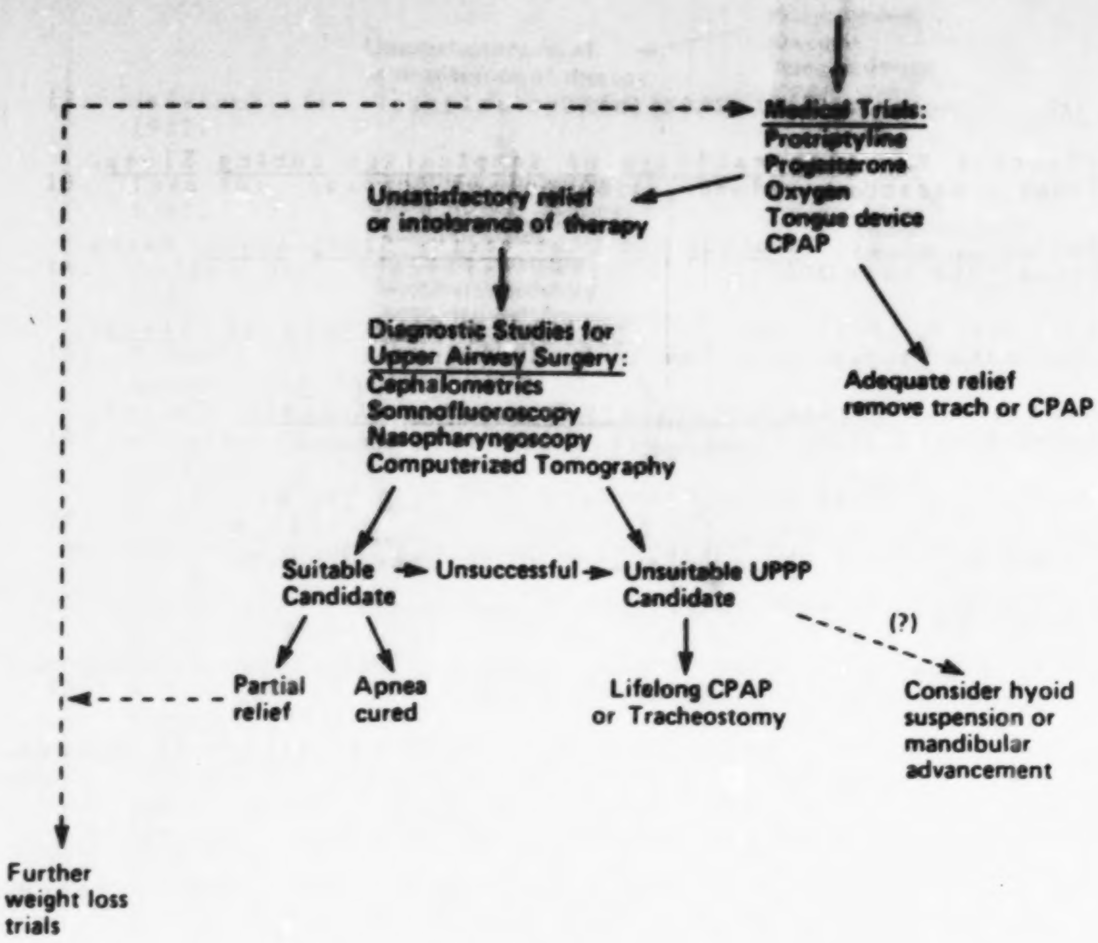
A frequently misunderstood issue is the need for a full overnight sleep study to determine the correct level of CPAP; unfortunately, this requires a second visit to the sleep lab and entails additional expense. Since collapsing forces are greatest in REM sleep (maximal between 4-6 a.m.), if a patient is treated with the minimum pressure level required to prevent apnea in NREM sleep, partial obstruction may occur with REM sleep onset. This causes hypoventilation with gradually worsening hypoxemia and hypercarbia undefended by active arousal responses during the 7-10 day "rebound" period. Patients with concomitant COPD seem to be at particular risk for this potential complication.

Another role for nasal CPAP is in reducing perioperative morbidity in obstructive sleep apnea patients. Because of the rebound phenomenon with depressed arousal responses, etc., patients undergoing UPPP were often tracheostomized as well, to prevent perioperative catastrophe from anesthetics, sedatives, etc., before the clinical benefits from UPPP could be realized. Nasal CPAP safely obviates the need for a second morbid procedure.

SUMMARY

See attached treatment protocols


History, physical, laboratory data
< 100 Apneas per night
Nadir SaO_2 above 85%
> 150 Apneas per night
Nadir SaO_2 below 80%
Asymptomatic
Mild symptoms
Moderate or severe symptoms
Inconsequential Arrhythmias
No cardiac or pulmonary dysfunction
Normal daytime blood gases
Apnea related, life-threatening arrhythmias
Cardiac dysfunction, COPD
Daytime Alveolar Hypoventilation
Avoid alcohol and sedatives at bedtime
Eliminate anatomic or treat medical causes of apnea
"ROUTINE"
"URGENT"
Refuses tracheostomy
Cannot tolerate CPAP
CPAP or tracheostomy
Not overweight
Not position dependent
Overweight (> 150% IBW)
or Position dependendent
Final therapy
1. "Older" patient
2. Longevity limited by other disease
Dietary weight loss or position device
Unsuccessful
Apnea cured remove Trach or CPAP
Partial relief
Gastric stapling
Not cured or partial success
Apnea cured remove Trach or CPAP
Medical Trials


Medical Trials:
Protriptyline
Progesterone
Oxygen
Tongue device
CPAP
Unsatisfactory relief
or intolerance of therapy
Adequate relief
remove trach or CPAP
Diagnostic Studies for
Upper Airway Surgery:
Cephalometrics
Somnofluoroscopy
Nasopharyngoscopy
Computerized Tomography
Suitable
Candidate
Unsuccessful
Unsuitable UPPP
Candidate
(?)
Partial
relief
Apnea
cured
Lifelong CPAP
or Tracheostomy
Consider hyoid
suspension or
mandibular
advancement
Further
weight loss
trials

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DIFFUSE INTERSTITIAL LUNG DISEASE

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INTRODUCTION

In 1944, Hammen and Rich reported a group of patients with a rapidly progressive, diffuse, fibrosing process of the lungs (1). Since that time, the label of "interstitial lung disease" has been given to the pulmonary component of a large group of syndromes which vary by etiology but share a final common pulmonary histopathologic state--diffuse fibrosis of lung parenchyma.

The purpose of this review is to describe the histopathology and clinical presentation of fibrotic lung disease and to discuss available therapy.

HISTOPATHOLOGY

Histopathologically, fibrosis of the alveolar interstitium is a process common to all of the interstitial lung diseases (2,3,8). Additionally, a chronic alveolitis is present (hence the term favored by the British for interstitial fibrosis--fibrosing alveolitis). The alveolitis leads to a derangement of alveolar structures resulting in a loss of functional gas exchange units. The basic process is inflammatory, with fibrosis being an "end-stage" condition.

Liebow attempted to categorize the alveolitis of interstitial lung disease by the cell type present in the interstitial and alveolar spaces (2). His work has resulted in "alphabet soup" labels for the pathologic processes seen. Some authors find this system unnecessary and confusing. However, since they are in common use, the histopathologic entities are presented here, as follows:

A. Usual Interstitial Pneumonia (UIP) -- Interstitial infiltration of monocytes and lymphocytes and occasionally other inflammatory cells. Fibroblastic activity and fibrosis constitute the most common histopathologic picture seen in interstitial lung disease.

B. BIP -- Bronchiolitis obliterans superimposed on a UIP histopathologic picture. Seen in toxic inhalation such as chlorine gas or smoke inhalation and in viral infection.

C. Desquamative Interstitial Pneumonia (DIP) -- Differs from usual interstitial pneumonia in that there is proliferation of macrophages with accumulation of these cells in the alveolar spaces. Lung parenchyma is not disturbed by necrosis or loss of tissue. DIP may be seen in any syndrome in which UIP is found. Different sections of the same pathology specimen may demonstrate UIP and DIP.

D. Lymphoid Interstitial Pneumonia (LIP) -- Infiltration of the interstitium with lymphoid cells in a pattern similar to lymphoma with varying admixtures of plasma cells and other elements. LIP may appear in association with pernicious anemia, Sjogren's syndrome, dysproteinemia, and macroglobulinemia. LIP and pseudolymphoma can be used interchangeably; however, the diagnosis of pseudolymphoma is usually reserved for a localized lesion.

E. Giant Cell Interstitial Pneumonia (GIP) -- Infiltration of large and small mononuclear cells with large numbers of phagocytic giant cells.

F. Eosinophilic Interstitial Pneumonia (EIP) -- This condition may be associated with asthma, drug exposure. and parasitic infestations such as filariasis and ascariasis. Alveolar walls are thickened with focal areas of fibrosis. An interstitial eosinophilic response is present and eosinophils appear in the alveoli.

UIP is often referred to as the histopathologic lesion of idiopathic pulmonary fibrosis (2). However, similar pathologic changes have been seen in lung damage from drug toxicity, collagen diseases and viral pneumonias. Any of the syndromes in which progressive interstitial pulmonary fibrosis is seen can be manifest histologically as UIP (14). DIP is felt by some to represent an earlier stage in the development of UIP pathology (10). It is still not known whether UIP, DIP or BIP are specific lesions or different aspects of the same fibrosing alveolitis. The distinction seems to be worthwhile clinically as response to therapy may vary among the different classifications (19).

PATHOGENESIS

One scheme of pathogenesis postulates an initial agent or stimulus leading to release of chemical mediators and infiltration by inflammatory cells (2,29,30). Inciting factors have been defined in some types of pulmonary fibrosis but not in all. Alveolitis with derangement of alveolar structure and fibrosis results if the process proceeds unchecked. Evidence supporting this scheme includes the following clinical observations:

A. Biopsies "early" in the disease state may show alveolitis without fibrosis (2).

B. Serial biopsies over time may show progressive inflammation prior to fibrosis (2).

C. Cell types found during the alveolitis stage have the ability to produce mediators such as collagenases and elastases (6).

D. Patients with idiopathic pulmonary fibrosis have been shown to have elevated levels of collagenase in washings of the lower respiratory tract when compared to normals (6).

E. Circulating immune complexes have been found in patients who on lung biopsy are in the inflammatory stage of interstitial lung disease (7).

F. Positive immunofluorescent studies of lung biopsies in patients with idiopathic pulmonary fibrosis who have high titer ANAs or circulating immune complexes suggest immune mechanisms are responsible (8).

G. Marked increases in IgG secreting cells in the bronchoalveolar lavage fluids of patients with active interstitial lung disease have been described (9).

Thus, the histopathology seen in the diseases leading to interstitial fibrosis most likely is generated by an inflammatory response mediated by immunoglobulins and the immune system in general. A majority of available evidence suggests that the immunologic derangement is compartmentalized, or restricted to the lung (30). The exact pathophysiology of the process and the reason(s) why the process proceeds in some syndromes when the initial stimulus is withdrawn remains unknown. A review on the pathogenesis of interstitial lung disease has recently been published (35).

ETIOLOGY

Approximately 130 defined syndromes lead to pulmonary fibrosis. Of these, about 35% have a known etiology. Tables 1a and 1b, which are adapted from Crystal (2), illustrate the diversity of syndromes associated with diffuse interstitial pulmonary fibrosis (2). When the clinical condition of diffuse pulmonary fibrosis exists and no such association can be made the label of idiopathic pulmonary fibrosis is given. This diagnosis is always one of exclusion. Every patient presenting with signs and symptoms of interstitial lung disease must undergo a careful evaluation to rule in or out known (and potentially treatable) etiologies. Since a histologic picture of UIP can be seen in any of the syndromes listed in Tables 1a and 1 b, in many cases exact diagnosis relies more on history and clinical evaluation than on the biopsy itself. Additional findings on biopsy may, however, support a specific diagnosis. For example, sarcoidosis will show granuloma formation in addition to alveolitis and fibrosis.

CLINICAL PRESENTATION

Patients with diffuse interstitial lung disease present with a common group of signs and symptoms which are attributable to the derangement of lung architecture and physiology caused by the underlying inflammatory/fibrotic process (2-5,11,12,14-16,23). Additionally, they may have signs and symptoms attributable to the inciting process. Most patients present with the insidious onset of breathlessness, occasionally associated with a non-productive cough. The most common physical finding is bibasilar, "dry" (or "velcro") end-inspiratory rales. Clubbing of the fingers is frequently seen. A minority of patients are relatively asymptomatic and are picked up on routine screening chest x-rays. Asymptomatic tachypnea is often present at rest. Sputum, if present at all, is typically neither copious or purulent. Cor pulmonale may be manifested in later stages. Polycythemia is unusual. Pleural disease is found only in association with diseases known to have pleural manifestations. Positive ANAs, abnormal serum proteins, cryoglobulins, and positive rheumatoid factors can be found in many patients with progressive fibrosis, even when disease is not felt clinically to be secondary to a specific connective tissue disorder.

CHEST X-RAY IN INTERSTITIAL LUNG DISEASE

The chest x-ray in interstitial lung disease typically shows a diffuse interstitial infiltrate throughout the lungs (25). However, the chest x-ray may be normal in up to 10% of the patients at the time of presentation (24).

The following general patterns of infiltrate have been described (3):

A. Nodular or ill-defined densities

B. "Ground glass" appearance

C. Reticular-nodular pattern

D. Reticular pattern with randomly oriented linear densities.

E. "Honeycomb" pattern with coarse reticular densities and translucencies.

These patterns are nonspecific and can be associated with many of the syndromes described. There are syndromes however which are associated with additional x-ray abnormalities (i.e. hilar adenopathy in sarcoidosis or pleural plaques in asbestosis).

PULMONARY FUNCTION TESTS IN DIFFUSE LUNG DISEASE

Interstitial lung disease with parenchymal fibrosis causes an increase in elastic recoil of the lungs and decreased compliance (stiff lungs). The alterations in lung mechanics and V/Q relationship have been well described (18). Classically, pure interstitial lung disease causes a reduction in all lung volumes. DL/VA, which relates the loss of perfused space to the loss of ventilated space, may or may not be decreased, depending upon the predominance of fibrosis in either compartment. Desaturation of arterial blood on exercise is characteristic of interstitial lung disease since lung V/Q may not improve with exercise due to the fibrotic nature of the disorder. (In many other chronic lung conditions, V/Q mismatching improves with exercise since the additional cardiac output perfuses areas of high V/Q ratios.) Patients with interstitial fibrosis may be unable to effectively increase cardiac output with exercise due to high pulmonary vascular resistance. Any increase they are able to generate may well go to areas of the lung where the fibrotic process has severely altered V/Q ratios.

DIAGNOSIS OF DIFFUSE INTERSTITIAL LUNG DISEASE

Since the diagnosis of interstitial lung disease is a histologic diagnosis, invasive procedures are frequently required. A careful history and physical along with chest x-ray, PFTS, rest and exercise arterial blood gases, and screening lab tests are prerequisites for biopsy. The tissue diagnosis should serve two purposes:

A. To confirm the presence of a process of inflammation and fibrosis in the lung tissue sample.

B. To look for other characteristic changes, such as granuloma formation, which would characterize the interstitial process into one of the known etiologic or associated groups.

Tissue can be obtained by transbronchial biopsy or by open lung biopsy. Usually only sarcoidosis, eosinophilic granuloma, or lymphangitic carcinoma can be safely diagnosed by transbronchial biopsy, since these have reasonably specific lesions which can be identified in the small specimens obtained through the bronchoscope. Most interstitial diseases are classified by morphologic characteristics identifiable on low-power microscopy of large sections, whereas examination of small segments may show only non-specific infiltrates and/or fibrosis, with a good deal of variability from one area to another (27). Therefore, an open lung biopsy is often necessary to make the diagnosis.

In many syndromes such as the pneumoconioses, granulomatous diseases, hypersensitivity states, etc., specific histopathology is described in articles dealing with each syndrome. Several state-of-the-art articles are listed in the bibliography for this section (11-13,15,16). The subject of specific histopathology is too broad to be covered in this short review (see other sections).

Two new diagnostic (and management) techniques have been recently described. Although they appear useful their value in diagnosis and management remains unproven.

A. Bronchoalveolar Lavage -- This technique is championed by Ronald Crystal who feels that the procedure is an integral part of diagnosis and management of interstitial lung disease (21,26). The basic assumption is that even though the end-stage appearance of the interstitial lung disorders is similar in many diseases, the alveolitis stage varies from disorder to disorder and can be characterized by the types of inflammatory and effector cells present. Lavage fluid is instilled into a subsegmental bronchus via a "wedged" bronchoscope. In the typical interstitial lung disease patient approximately 50% of the fluid is recovered. Cell counts and differentials are obtained from the fluid. Cells and proteins obtained in this manner come from the alveolar epithelial surface and are assumed to be similar in type, proportion, and function to the effector components within the alveolar interstitium. In non-smoking normal subjects, approximately 93% of the cells obtained are alveolar macrophages with the rest being lymphocytes. Less than 1% of the cells in normal subjects are neutrophils, eosinophils or basophils. Differentials for normal smokers are similar except for slightly increased numbers of neutrophils. Lavage fluids of patients with idiopathic pulmonary fibrosis usually have increased neutrophils with a normal population of lymphocytes. Lavage fluid of patients with hypersensitivity pneumonitis and sarcoidosis usually have increased numbers of lymphocytes, with neutrophils rarely being present except in smokers. Currently, neutrophil differentials of greater than 10% are felt to be most consistent with idiopathic pulmonary fibrosis while lymphocyte differentials of greater than 15% are more consistent with sarcoidosis or hypersensitivity pneumonitis. The absolute cell count is not used since there may be wide variation in total numbers of cells obtained according to the amount of fluid instilled and the success in fluid retrieval. Some caution in interpreting lavage findings is necessary since inflammatory airway disease may increase the neutrophil count. Recent studies have also shown increased proportions of lymphocytes in lavage fluid in patients with lymphoma and tuberculosis. A lack of concordance between lavage fluid analysis and semiquantitative analysis of biopsy material further limits lavage in diagnosis and staging of interstitial lung disease. However, serial lavage analysis may be useful in monitoring patient response to therapy. Patients with idiopathic pulmonary fibrosis who respond to therapy show a trend to normalization of lavage cell counts (31). Lavage fluid findings in general are only supportive and current practice still requires tissue biopsy for initial diagnosis.

B. Gallium Scanning -- Gallium is a radionuclide which localizes in sites of inflammation. Gallium does not localize in normal lung tissue. Abnormal gallium uptake has been described in infectious, neoplastic, toxic, vasculitic, and idiopathic lung disorders. Most interstitial lung diseases have been noted to be associated with positive gallium scans. Usually diffuse uptake is noted but mixed focal and diffuse patterns may be seen. The gallium scan is suggestive but not specific. Assessment of the degree of abnormality remains qualitative, not quantitative. Whether or not the degree of abnormality of the gallium scan accurately reflects the intensity of the alveolitis has been debated. Currently, gallium scanning is used as an interesting adjunct in the management of patients with interstitial lung disease, supplying supportive information to the decision-making process.

TREATMENT OF INTERSTITIAL LUNG DISEASE

The treatment of interstitial lung disease has remained controversial (2-4,19-22,28). Problems which make assessment of therapy difficult include the following:

A. The etiology of the interstitial process is known in only 35% of the cases. Comparing treatment of disease processes of different etiology which have common pathophysiology is difficult. Therapy is non-specific for diseases of unknown etiology. Two separate diseases may share a common pathophysiologic presentation yet differ markedly in natural history and response to therapy.

B. Classification of the interstitial lung diseases remains inexact. Histopathology shows overlap from one syndrome to another, and a standard classification scheme has not been universally accepted. A single syndrome may be classified differently by separate investigators.

C. Most of the studies available regarding treatment and prognosis describe patients with idiopathic pulmonary fibrosis. Little work has been done to study subgroups of patients whose fibrosis is associated with syndromes such as the collagen-vascular diseases. It remains unclear whether the UIP associated with these syndromes responds to treatment similarly to the UIP seen in idiopathic fibrosis.

D. In those patients treated with immunosuppressants and steroids, the drug treatment regimen has not been standardized from study-to-study.

E. It has been difficult to assign a staging classification to the fibrotic process. Though some authors feel response to therapy is best in patients treated "early" in their disease, the definition of "early" versus "late" remains imprecise.

In patients whose progressive fibrosis is associated with a disease of known etiology such as tuberculosis, treatment is directed toward the agent responsible. Likewise, withdrawal of offending agents such as the thermophilic actinomycetes responsible for hypersensitivity pneumonitis is standard therapy. In the vast majority of cases where specific therapy is not available, potential therapeutic agents usually fall into one of two categories:

A. Corticosteroids -- Several studies have shown a beneficial effect of corticosteroid therapy in idiopathic pulmonary fibrosis (19,20,22,28). In general, patients whose disease has an active inflammatory component respond better than patients with end stage fibrosis. Patients whose pathology specimen has a DIP picture have one-half the mortality of patients with UIP, with a mean survival double that of the UIP population. With corticosteroid therapy, 60% of patients with DIP may improve, compared to only 10-11% of UIP patients. In addition, patients with an increase in lavage lymphocytes and idiopathic pulmonary fibrosis respond better to corticosteroids (32). The role of corticosteroids in the interstitial diseases associated with the collagen vascular syndromes remains poorly defined. In diseases such as histiocytosis-x and lymphangitic carcinomatosis where the effector cells which presumably modulate the inflammatory response are not steroid sensitive, response to steroids is predictably low.

There is no standard corticosteroid regimen for interstitial lung disease. The regimen described by Crystal et al from the NIH group is as good as any (2). Therapy is started 2-4 weeks after open lung biopsy with prednisone at 1 mg per kilogram per day. This dose is tapered after 6 weeks by 2 1/2 mgs/day each week until a maintenance dose of .25 mg per kilogram per day is reached. At that time further treatment is based on gallium scanning and bronchial lavage (procedures which seem promising but have not been validated) in addition to PFT's, chest x-ray and symptomatology. The steroid is tapered if the alveolitis appears to be resolving or disappears. Failure to respond directs another high dose trial of 1 mg per kilogram per day for 6 weeks followed by a retrial of tapering dosage.

B. Immunosuppressive Agents -- The role of immunosuppressive agents in interstitial lung disease is less well defined than that of corticosteroids. Because of its unproven status, immunosuppressive therapy is nearly always reserved for patients who have failed corticosteroid therapy and have severe physiologic derangement from their interstitial process. Therefore most patients fall into a "last-ditch effort" group and are biased toward a poor prognosis and therapeutic response. Penicillamine, cyclophosphamide, chlorambucil, azathioprine, and vincristine have all been tried (alone or with corticosteroids) in idiopathic pulmonary fibrosis. A double blind, randomized trial using azathioprine as an adjunct to corticosteroids in idiopathic pulmonary fibrosis showed no difference between therapies over one year (28). Interestingly, both cyclophosphamide and penicillamine have been described as causing interstitial lung disease. Cyclophosphamide is effective in treating Wegener's granulomatosis; this is a special case, however, since Wegener's is a vasculitis-type disease. Preliminary results of an ongoing double-blind, controlled trial of Cytoxan and low dose prednisone compared with high dose prednisone in idiopathic pulmonary fibrosis suggest a survival advantage in the cyclophosphamide group (31).

HEART-LUNG TRANSPLANTATION

In selected young (<50 years old) patients with end stage fibrosis, combined heart-lung transplantation may offer prolonged survival (33,34).

CONCLUSION

The syndromes associated with interstitial lung disease are difficult to treat. The clinical picture which represents the final common pathophysiologic expression of these entities is well described and not difficult to diagnose. Treatment will remain on unsure footing until the etiologic and pathophysiologic aspects of each of the syndromes is well defined. Until then, management will remain analogous to that of infectious diseases prior to the golden age of bacteriology -- empiric and imperfect.

TABLE 1a. INTERSTITIAL LUNG DISEASES OF KNOWN ETIOLOGY
Occupational and Environmental Inhalants

Inorganic dusts
- Silica
- Silicates
  - Asbestos
  - Talc
  - Kaolin
  - Sillimanite
  - Diatomaceous earth
  - Nepheline
  - Mica
- Aluminum
  - Powdered aluminum
  - Bauxite
- Antimony
- Carbon
  - Coal dust
  - Graphite
- Beryllium
- Mixed dusts
- Hard metal dusts
  - Titanium oxide
  - Tungsten, titanium, hafnium, and nobium carbides
  - Cadmium

Organic dusts
- Living sources
  - Farmer's lung
  - Bagassosis
  - Mushroom worker's lung
  - Humidifier lung, air conditioner lung
  - Maple bark stripper's lung
  - Cheese worker's lung
  - Malt worker's lung
  - Sequoiosis
  - Paprika splitter's lung
  - Wheat weevil disease
  - Suberosis
  - Bird breeder's lung
  - Chicken handler's disease
  - Aspergillosis
  - Pituitary snuff lung
  - Turkey handler's lung
  - Duck fever
  - Wood-pulp worker's disease
  - Sauna-taker's disease
  - Detergent worker's lung
  - Lycoperdonosis
  - Wood-dust worker's disease
  - Coffee worker's lung
  - Furrier's lung
  - New Guinea lung
  - Coptic disease
  - Japanese "summer type"

Organic dusts cont'd
- Chemical sources
  - Synthetic-fiber lung
  - Bakelite worker's lung

Gases, fumes, vapors, aerosols
- Gases
  - Oxygen
  - Sulfur dioxide
  - Chlorine gas
- Fumes
  - Oxides of zinc, copper, manganese, cadmium, iron, magnesium, nickel, brass, selenium, tin and antimony
- Vapors
  - Mercury
  - Thermosetting resins
  - Toluene diisocyanate
- Aerosols
  - Fats
  - Pyrethrum
  - Copper sulfate neutralized with hydrated lime

Drugs
- Chemotherapeutic agents
  - Busulfan
  - Bleomycin
  - Cyclophosphamide
  - Methotrexate
  - Nitrosoureas (BCNU)
  - Procarbazine
  - Mitomycin
- Antibiotics
  - Nitrofurantoin
  - Sulfonamides
  - Penicillin
- Others
  - Diphenylhydantoin
  - Drugs inducing lupus-like syndrome
  - Gold salts
  - Hexamethonium
  - Mecamylamine
  - Methysergide
  - Pentolinium
  - Propranolol
  - Carbamazine

Poisons
- Paraquat

Radiation
- External
- Inhaled

Infectious agents
- Residue of active infection of any type

Table 1b INTERSTITIAL LUNG DISEASE OF UNKNOWN ETIOLOGY

- Idiopathic pulmonary fibrosis

- Chronic interstitial disease associated with the collagen-vascular disorders

  - Rheumatoid arthritis
  - Progressive systemic sclerosis
  - Polymyositis-dermatomyositis
  - Sjogren's syndrome
  - Overlap syndrome

- Sarcoidosis
- Histiocytosis-X
- Goodpasture's syndrome
- Idiopathic pulmonary hemosiderosis
- Wegener's granulomatosis
- Lymphocytic infiltrative disorders
  - Lymphomatoid granulomatosis
  - Immunoblastic lymphadenopathy
- Unclassified

- Vasculitides

  - Churg-Strauss syndrome
  - Hypersensitivity angitis
  - Overlap
- Inherited disorders

  - Tuberous sclerosis
  - Neurofibromatosis
  - Familial pulmonary fibrosis

- Pulmonary veno-occlusive disease
- Ankylosing spondylitis
- Diffuse amyloidosis of lung
- Chronic eosinophilic pneumonia
- Lymphangioleiomyomatosis
- Whipple's disease
- Weber-Christian disease
- Hermansky-Pudlak syndrome

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SARCOIDOSIS

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DEFINITION

Sarcoidosis is a systemic disease characterized by the presence in all of several affected organs and tissues of non-caseating epithelioid cell granulomas, proceeding either to resolution or to conversion into featureless hyaline connective tissue (1).

ETIOLOGY

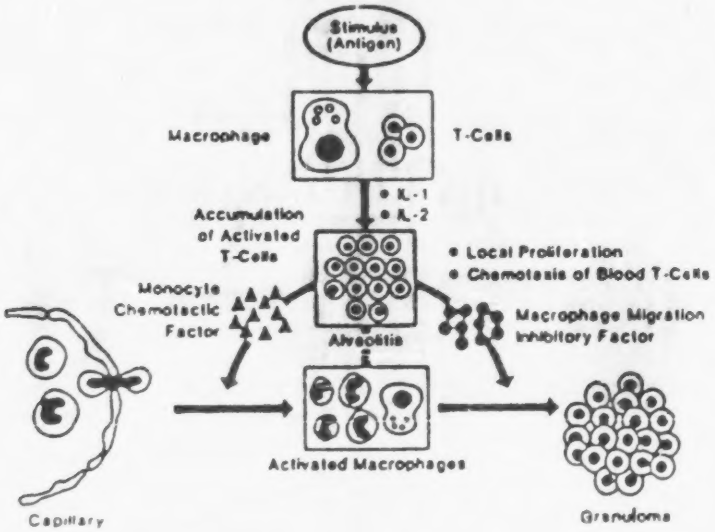
The etiology of sarcoidosis remains unknown. Multiple theories have been proposed. Most postulate either an inherited or an acquired defect in some aspect of the patient's immune response. HLA antigens, particularly B7, B8, BW15, and BW40 have been reported in greater numbers of sarcoid patients than controls; however, these antigens probably have no bearing on the occurrence of disease (2). Mitchell and Scadding have suggested that patients with sarcoidosis have abnormal immunologic responses, but no one has been able to demonstrate an immunologic abnormality prior to onset of sarcoidosis (1). Mitchell and Rees injected homogenates of sarcoid nodes into mice foot pads, intraperitonealy and intravenously, with resultant granuloma formation in the injection sites. These data suggest a transmissible agent, (which could be an animate one), a lymphokine, or some other informational macromolecule (3). Older theories which have received less recent attention are pine pollen exposure and host susceptibility to phage infected mycobacteria as a result of phage neutralizing antibody deficiency (1).

EPIDEMIOLOGY

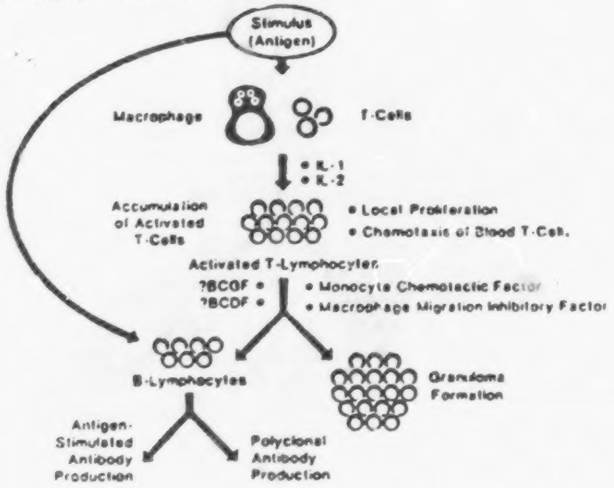
Sarcoidosis is a disease of worldwide distribution but appears to be more common in temperate areas such as the USA, Great Britain, and Scandinavia. It is quite rare among orientals but 12-15 times more common in US blacks than whites. Interestingly, it is very rare among non-USA blacks. Over two-third's of those affected are less than 40 years old.

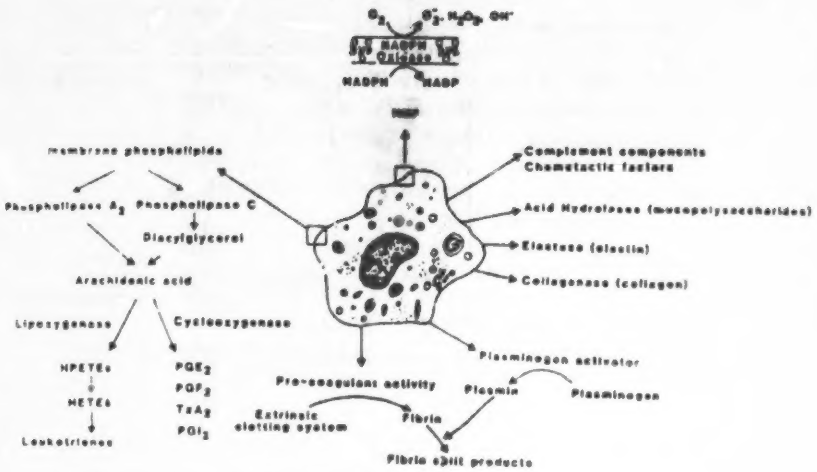
IMMUNOLOGY

Important strides in understanding sarcoidosis have recently been made. Crystal et al, with the use of bronchoalveolar lavage have demonstrated that sarcoidosis begins as an interstitial lymphocytic infiltrate consisting of T-cells in which "helper T-cells" are present to excess and outnumber "suppressor T-cells" by a ratio of 10:1. The "helper T-cells" secrete lymphokines which augment B-cell function leading to hypergammaglobulinemia. These lymphokines also attract monocytes which can further differentiate into alveolar macrophages, resulting in alveolitis and granuloma formation. As relatively larger numbers of "suppressor T-cells" remain in the peripheral blood, it is theorized that this phenomenon may in some way explain the cutaneous anergy of sarcoidosis (4,5). The following figures illustrate the pathogenesis of granulomatous disorders, the prototype of which is sarcoidosis, and how alterations in the immune system can lead to granuloma formation, hypergammaglobulinemia, and collagen deposition leading to parenchymal fibrosis and structural derangement. The figures also illustrate the critical role of the alveolar macrophage in the pathogenesis of these diseases (Pathogenesis of granulomatous lung diseases ARRD 130:476, 1984).

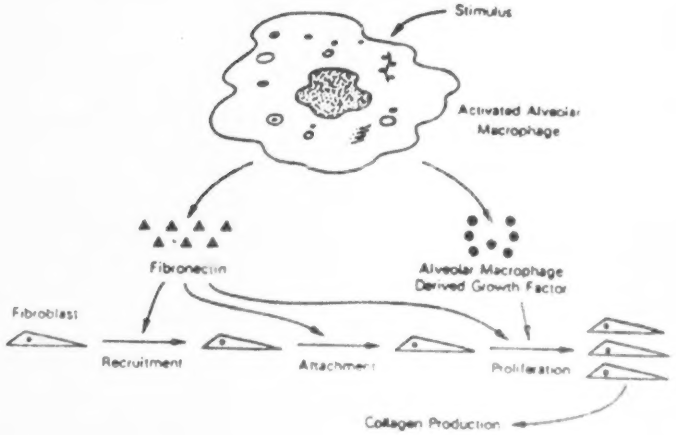

Stimulus (Antigen)
Macrophage
T-Cells
• IL-1
• IL-2
Accumulation of Activated T-Cells
• Local Proliferation
• Chemotaxis of Blood T-Cells
Monocyte Chemotactic Factor
Macrophage Migration Inhibitory Factor
Alveolitis
Activated Macrophages
Capillary
Granuloma

Pathogenesis of granuloma formation


Stimulus (Antigen)
Macrophage
T-Cells
• IL-1
• IL-2
Accumulation of Activated T-Cells
• Local Proliferation
• Chemotaxis of Blood T-Cells
Activated T-Lymphocytes
?BCGF •
?BCDF •
• Monocyte Chemotactic Factor
• Macrophage Migration Inhibitory Factor
B-Lymphocytes
Granuloma Formation
Antigen-Stimulated Antibody Production
Polyclonal Antibody Production


O_2
O_2^-, H_2O_2, OH^-
NADPH Oxidase
NADPH
NADP
Membrane phospholipids
Phospholipase A_2
Phospholipase C
Diacylglycerol
Arachidonic acid
Lipoxygenase
Cyclooxygenase
HPETEs
HETEs
Leukotrienes
PGE_2
PGF_2
TxA_2
PGI_2
Complement components
Chemotactic factors
Acid Hydrolases (mucopolysaccharides)
Elastase (elastin)
Collagenase (collagen)
Plasminogen activator
Pro-coagulant activity
Plasmin
Plasminogen
Extrinsic clotting system
Fibrin
Fibrin split products

Mechanisms of macrophage-mediated tissue injury.


Stimulus
Activated Alveolar Macrophage
Fibronectin
Alveolar Macrophage Derived Growth Factor
Fibroblast
Recruitment
Attachment
Proliferation
Collagen Production

CLINICAL MANIFESTATIONS

Although histologic involvement occurs in many organs, clinical dysfunction is usually limited to the lung. Pulmonary involvement has been customarily "staged" by the appearance of the radiograph. These arbitrary "stages" may correlate poorly with functional status or degree of inflammatory activity as assessed by bronchoalveolar lavage (BAL), lung biopsy or pulmonary functions.

Stage I	- Bilaterally symmetrical hilar adenopathy with or without right paratracheal/ductus nodal adenopathy. No parenchymal infiltrates (alveolitis may be present even though undetectable radiographically)	38 to 45% initial presentation
Stage II	- BHA with pulmonary infiltrate	24 to 50% initial presentation
Stage III	- Parenchymal infiltrates without BHA	8 to 15% initial presentation
Stage IV	- Recognized by some authors, essentially a far-advanced Stage III with parenchymal destruction and scarring.	

Pleural involvement, once thought to be virtually non-existent in sarcoidosis, has more recently been shown to be present in approximately 10% of those patients with parenchymal infiltrates. It may present as pleural thickening or pleural effusion and pleural biopsies may yield non-caseating granulomata (6). Both transudative and exudative lymphocytic pleural effusions have been reported. Unilateral hilar adenopathy is rare (approximately 2%) and should suggest another diagnosis, e.g. lymphoma, carcinoma or infection. Sarcoidosis can occasionally present with alveolar and/or nodular infiltrates on chest radiograph. These infiltrates may mimic chronic eosinophilic pneumonia with its "classic" radiographic picture of reverse pulmonary edema pattern. (Glazer et al, Chest 86-5:741, 1984). A type of sarcoidosis which produces cavitary infiltrates has been described and probably represents a form of vasculitis from granulomatous invasion of pulmonary vessels (Sharma O.P, Postgrad Med 61:67, 1974; Kirks D.R., AJR 117:777, 1973).

The following table illustrates the incidence of sarcoidosis in various organ systems. It is important to keep in mind that these percentages are derived from series of patients referred to large academic institutions and therefore tend to be biased toward patients with more severe disease.

Table 1. Estimated frequency of clinical involvement of extrathoracic organs in sarcoidosis. (Compiled from the data of Maycock, et al.)

Extrathoracic Organs	%
Peripheral lymph nodes	73
Skin	32
Liver	21
Eye	21
Spleen	18
Bone	14
Salivary glands	6
Joints	6
Heart	5
Nervous system	5
Kidneys	4
Nose and mouth	3
Lacrimal glands	3
Skeletal muscle	1
Larynx	1
Stomach and intestine	1
Uterus	1

DIAGNOSIS

The workup for sarcoidosis should exclude other diseases similar to sarcoid, assess specific organ dysfunction, possibly attempt to assess the intensity of the alveolitis, and provide a baseline for follow-up as illustrated.

Sarcoidosis Diagnostic Evaluation (7)

- CBC, ESR
- LFTS, BUN, creatinine, calcium, uric acid, 24-hour urine for calcium
- Tuberculin, coccidioidin, and anergy skin tests
- Sputa for AFB and fungal smear/culture
- Fungal serologies (of limited utility in most cases)
- Ophthalmology exam including slit-lamp exam
- PFT's with ABG's and DLCO

- **Histologic study of appropriate biopsies:**
    - **conjunctiva**
    - **skin**
    - **bronchus**
    - **pulmonary parenchyma**
    - **mediastinal nodes**
    - **salivary glands**

- **Angiotensin converting enzyme**

- **Gallium scan+**

- Other possible tests:
    - Kveim*
    - Bronchoalveolar lavage+

*Not available for ordinary clinical use
+May be of value assessing disease activity, clinical utility still controversial)

Certain sites of histologic assay merit further discussion. Slit-lamp examination has been reported to visualize conjunctival lesions undetectable to the naked eye, particularly in blacks, which _if_ _seen_ are histologically positive for non-caseating granulomata in 38-57% of blacks (8). Overall, conjunctival biopsies are positive in 30-40% of cases regardless of stage. (Solomon D.A. et al, Chest 79:271, 1978)

Biopsy of lower lip minor salivary glands is a relatively painless and non-invasive method for establishing the diagnosis, and in a recent study yielded diagnostic tissue in 58% of 75 subjects (9). It is a "blind" procedure, however, in that no physical findings are present to aid in the selection of patients for biopsy. A recent study from our institution showed that sarcoidosis can be diagnosed by parotid gland biopsy in approximately 55% of patients. In this study, patients with parotid glands uptake by Ga++67 scanning had a slight but non-significant increase in diagnostic yield (Chest 91(3):403, 1987).

If a superficial site such as skin or mucous membrane is unavailable, transbronchial lung biopsy is usually considered to be the procedure of choice. The diagnostic yield appears to be proportional to the number of biopsies taken and to the degree of infiltration in the area biopsied. When ten biopsies were taken the diagnostic yield in one study was shown to be 97% with a diagnosis established in 100% of subjects with Stage I disease (10). Other studies suggest that the diagnostic yield plateaus after approximately 6-8 biopsies and is increased if biopsies are taken from different lobes or segments. The following table summarizes the diagnostic yield of bronchoscopy with transbronchial lung biopsy in sarcoidosis.

Transbronchial Biopsy in Sarcoidosis

Percentage of pts with positive
findings on biopsy by stage

	Stage 1	Stage 2	Stage 3	*All Stages
Koerner	6/8 (75%)	6/6 (100%)	8/8 (100%)	21/23 (91%)
Koontz, 76	11/20 (55%)	11/15 (73%)	2/3 (67%)	24/38 (63%)
Khan	6/7 (86%)	10/12 (83%)	3/4 (75%)	20/24 (83%)
Teirstein	6/8 (75%)	17/20 (85%)	25/34 (74%)	48/62 (77%)
Bower	- -	- -	- -	12/16 (75%)
Koontz, 78	33/55 (60%)	33/39 (85%)	8/10 (80%)	74/104(71%)
Mitchell	2/3 (66%)	19/23 (83%)	14/14 (100%)	37/42 (88%)
Gilman	- -	- -	- -	12/12 (100%)
Roethe	10/10 (100%)	22/23 (96%)	4/4 (100%)	36/37 (97%)
Total	74/111 (66%)	118/138 (86%)	64/77 (83%)	284/358(79%)

* Koerner, Khan and Mitchell had four pts with "other" or with Stage 0 disease, 4/4 (100%).

(Koerner et al, NEJM 293:268, 1975) (Koontz et al, Ann Int Med 83:64, 1976) (Khan et al, NEJM 295:275, 1976) (Teirstein et al, Mount Sinai J. Med 44:740,1971) (Koontz et al, Chest 74:121, 1978) (Gilman et al, ARRD 122:721, 1980) (Roethe et al Chest 77:400, 1980).

Sarcoidosis is still occasionally diagnosed by mediastinal or paratracheal node sampling, especially in atypical cases where malignancy is suspected or when other diagnostic modalities have failed.

It has been suggested that not all cases of sarcoidosis require histologic confirmation. For many years most authorities concurred with a study by Winterbauer, et al, (11) which stated that a patient with a Stage I radiograph who is asymptomatic and has a normal physical exam could be assumed to have sarcoidosis. Now the pendulum appears to be swinging in the opposite direction. Thrasher, et al, evaluated 227 patients and found that a significant number of patients with infections and neoplastic disorders presented in a similar fashion. It was felt the danger of misdiagnosis exceeds the low morbidity associated with tissue diagnosis (29). The fact is that many times the decision to biopsy needs to be individualized e.g., one might consider following the asymptomatic patient with documented stable adenopathy for several years who lives in an area where histoplasmosis or coccidioidomycosis is rare. It is universally established, however, that tissue confirmation is necessary if treatment with corticosteroids is contemplated.

Angiotensin converting enzyme (ACE) is an enzyme found in high concentrations in endothelial cells of the lung. Its presence correlates better with thoracic sarcoidosis than with non-pulmonary sarcoidosis (28). Only about 60 percent of all patients with biopsy proven sarcoidosis have ACE elevations (29). Several studies have found no correlation between ACE levels and the degree of disease activity (5)(Roher et al Acta Med Scand 210:111, 1981) (Selroos O, Scan Journ Resp Diseases 60:328, 1979) (ARRD 126:631, 1983). The ACE level can be criticized as being non-specific as well. ACE levels are elevated in 9.5% of patients with tuberculosis and 3.5% of normals (15). It can also be elevated in leprosy, Gaucher's disease, and other diseases as illustrated in the following table.

TABLE 4.—DISEASES OTHER THAN SARCOIDOSIS THAT ARE ASSOCIATED WITH ELEVATED SACE LEVELS

CONDITION AND REFERENCE	TOTAL NO. (%) OF PATIENTS WITH ELEVATED-SACE LEVELS
Gaucher's disease[108]	9/9 (100.0)
Beryliiosis[109]	3/4 (75.0)
Hyperthyroidism[61, 62, 110]	63/93 (68.0)
Chronic renal failure or hemodialysis[65]	27/44 (61.0)
Talc granulomatosis[111]	3/6 (50.0)
Silicosis[57]	8/19 (42.0)
Leprosy[112]	32/95 (34.0)
Alcoholic liver disease[113]	43/151 (28.5)
Primary biliary cirrhosis[57]	19/71 (27.0)
Hypercalcemia[66]	
Oncogenic hypercalcemia	3/13 (23.0)
Hyperparathyroidism	4/35 (11.0)
Histoplasmosis[63, 64]	28/130 (22.0)
Diabetes mellitus[114, 115]	74/346 (21.0)
Extrinsic allergic alveolitis[57]	3/22 (14.0)
Asbestosis[57]	3/26 (11.0)
Coccidioidomycosis[112]	1/13 (7.0)
Tuberculosis[57]	5/140 (3.6)
Hodgkin's disease[57]	3/90 (3.0)
Asthma[57]	1/86 (1.5)
Primary lung cancer[57]	2/315 (0.6)
Chronic obstructive pulmonary disease[57]	1/209 (0.5)

Increased ACE levels have also been found in BAL fluid and tears of patients with sarcoidosis (Mordelet - Dombrine, ARRD 126:972, 1982; Sharma O.P. Arch Ophthalmol 101:559, 1983).

Gallium lung scanning appears to correlate well with the alveolitis of sarcoidosis as assessed by BAL lymphocyte counts and lung biopsy, and could serve as a means of following a patient on treatment. However, gallium scans are positive in only 60-65% of patients with active disease. Studies suggest that Ga++ citrate uptake correlates well with the macrophage stage of the alveolitis (Winterbauer, Current Pulmonology 7:136, 1986). Despite a relatively high sensitivity, the gallium scan's diagnostic utility is limited because of its poor specificity. Gallium may concentrate in the lungs of patients with lymphoma, tuberculosis, pneumonia or carcinoma. If gallium uptake is noted over the parotids and lacrimals, however, sarcoidosis is strongly suggested (16).

A recent study combined the ACE assay and gallium scanning to increase non-invasive diagnostic yields (99% diagnostic specificity if both are positive). The study was flawed, however, as the control group contained no patients with lymphoma and only one patient with tuberculosis (16).

Bronchoalveolar lavage (BAL) was adapted to fiberoptic bronchoscopy by Reynolds in 1974. It samples a large area of the lung, approximately 10^6 alveolar units during a typical procedure. Several studies suggest that cells recovered by BAL reflect those present on lung biopsy (Davies G. S. et al, ARRD 118:7, 1978) (Haslam P.O. et al Thorax 35:9, 1980). The procedure has been found to be safe and well tolerated by patients. In normal subjects (non smokers) 1.0-1.5 x 10^7 cells are recovered per ml of lavage fluid. Alveolar macrophages account for more than 90% of cells with lymphocytes less than 10% and neutrophils and eosinophils less than 1%. In smokers the number of cells increases almost twofold, with increases in the percentage of neutrophils.

Patients with active sarcoidosis typically show greater than 28% lymphocytosis, with most lymphocytes of the T-helper subtype. However, lymphocytosis is not unique to sarcoidosis and can be found in hypersensitivity pneumonitis, Pneumocystis carinii pneumonia, mycobacterial infections, talc granulomatosis, berylliosis, CMV infection, metastatic lung disease and idiopathic pulmonary fibrosis. Studies also suggest that smoking decreases lymphocyte counts in sarcoidosis.

High concentrations of IgG, IgA and IgG secreting cells have also been found in BAL of patients with sarcoidosis in addition to the high levels of ACE previously mentioned (Rankin JA, ARRD 127:442, 1983).

It is therefore apparent that BAL is of limited or no utility in establishing the diagnosis of sarcoidosis but may be of some value in evaluating disease activity either alone or in combination with Ga++ scanning.

PULMONARY FUNCTION CHANGES

Stage I disease may be accompanied by very mild alterations in the DLCO or A-a DO_2 (18). Overt parenchymal disease is frequently associated with more severe abnormalities of gas exchange including decreased O_2 saturation with exercise and reduced lung volumes. Patients with Stage III and Stage IV disease may actually have large and small airways obstruction either secondary to endobronchial sarcoidosis or (more likely) because of compression or traction on the airways by peribronchial fibrosis. With regards to following the vital capacity and DLCO in sarcoidosis, the following points should be remembered:

1. Approximately 80% of patients with Stage I disease have a normal FVC and 70% have a normal DLCO.

2. Approximately 35% of patients with parenchymal disease have a normal FVC and 34% have a normal DLCO.

3. There are no pulmonary function criteria that allow the clinician to predict the natural course of the disease or response to therapy.

4. Vital capacity and DLCO demonstrate a common direction of change in 2/3 of patients. One-third show change in only one of these functions. The vital capacity and DLCO change in opposite directions in less than 5% of patients.

5. Only 45% who improve radiographically and clinically show increases in DLCO. 5% will show decrease with improvement.

6. Most untreated patients will demonstrate no change or a decline in FVC and DLCO.

(Winterbauer R.H., Springmeyer S.C. - ACCP continued medical education series, 1985).

NATURAL HISTORY AND STAGING

Reports vary, but 60-80% of patients with Stage I, 46-60% of patients with Stage II, and 12-33% of patients with Stage III sarcoidosis experience spontaneous resolution of their illness (14). A recent study by Hillerdal suggests that it may take as long as 60 months for the chest radiograph to normalize in untreated patients with Stage I and II disease (ARRD 130:29, 1984). This information is of vital importance when assessing response to therapy and re-emphasizes that sarcoidosis is a relatively benign disease in the great majority of patients. Another recent study from a non-referral clinic setting at the Kaiser-Permanente Medical Care Program confirmed the good prognosis of the majority of patients affected with sarcoidosis

(AMJ 98:61, 1985). With the notable exception of the erythema nodosum- arthropathy syndrome, clinically significant extrapulmonary sarcoidosis is an unfavorable finding usually associated with disease progression. The following table summarizes some of the prognostic factors in sarcoidosis.

Table 2. Prognostic factors in sarcoidosis, based on the outcome of 818 patients. (Reprinted from Neville, et al.[4] Prognostic factors predicting the outcome of sarcoidosis: An analysis of 818 patients. *Quart. J. Med.* 52:525-533, 1983. With permission from Oxford University Press.)

Feature	Sarcoidosis Remission in 2 Yrs.	
	No.	%
Erythema nodosum	210/251	84
Acute arthritis	148/178	83
Hilar lymphadenopathy	334/458	73
Overall	467/818	57
Bilateral hilar lymphadenopathy with parenchymal infiltrates	77/150	51
Peripheral adenopathy	109/220	50
Lacrimals	11/22	50
Ocular	105/224	47
Spleen	35/100	35
Pulmonary infiltration	31/92	34
Heart	3/9	33
Parotid	15/52	29
Hepatomegaly	22/82	27
Central nervous system	19/77	25
Larynx	1/5	20
Lupus pernio	5/33	15
Involvement of upper respiratory structures	3/21	14
Bone	4/31	13
Nephrocalcinosis	0/10	0
Cor pulmonale	0/18	0

Over the last 10 years a number of clinical studies have attempted to identify subgroups of patients with sarcoidosis who are likely to deteriorate with time and who will benefit from therapy. (Rossman H.D. et al ARRD 125:366, 1982; Valey R.E.D. et al ARRD 126:41, 1982; Beamont D. et al Thorax 87:111, 1982; Valeyre et al, ARRD 129:428, 1984.; Keogh et al ARRD 128; 256, 1983; Colp, Med Clin North Am 61:1267, 1977; Abes et al, Chest 85:650, 1984; Baughman ARRD 129:676, 1984; Ceuppeus ARRD 129:563, 1984; Lawrence et al AMJ 74:747, 1983; Arnoux, Path Res Proct 175:62, 1982.) These studies have utilized angiotensin converting enzyme (ACE), gallium citrate lung scanning and recently, bronchoalveolar lavage (BAL) in addition to pulmonary function studies in order to "stage" the activity of the disease process. Overall, the results are conflicting and have failed to accurately define clinical subgroups with different therapeutic requirements. The most quoted article is that of Keogh et al (ARRD 128:256, 1983) from the National Lung Institute. Nineteen untreated patients were studied and followed at 6 month intervals with pulmonary functions, BAL and Ga++ citrate quantitative lung scans. Most patients were Stage II (14/17). The rest were Stage 0 or I and overall had mild abnormalities of pulmonary functions. Based on results of Ga++ scans (greater or less than 50 index units) and of T lymphocytes on BAL (greater or less than 28%), patients were classified as having either "high" or "low" intensity alveolitis. At the start of the study 5 patients were classified as "high" intensity alveolitis and 14 as "low" intensity alveolitis. Of note is the fact that the two groups did not differ from each other by chest radiographs or pulmonary function studies. Three of the 14 patients with "low" intensity alveolitis evolved to "high" intensity and 3 of 5 patients with high intensity alveolitis changed to the "low" intensity group. Most of the patients who had "high" intensity alveolitis at one point or another (6 of 8) reverted to "low" intensity. They noted that episodes of "high" intensity alveolitis were followed by pulmonary function deterioration (though generally mild) 87% of time while deterioration was seen in only 8% of the low intensity group. Though the authors of this study felt that staging the intensity of the alveolitis was of clinical utility in predicting the course of disease, many investigators argue that with more follow-up the pulmonary function of patients who changed from "high" to "low" groups would have probably also improved, with BAL and Ga scanning ultimately offering no advantage over conservative follow-up with pulmonary functions. Along these lines, a previous study by Colp had shown that the chance of "spontaneous" improvement was the same whether patients presented with vital capacities and DLCO greater than or less than 65% of predicted (Med Clin North Am 61:1267, 1971).

More evidence against the reliability of high intensity alveolitis or BAL as a predictor of outcome comes from a study by Valeyre who found a high incidence of alveolitis in patients with erythema nodosum and radiographic Stage I disease, a subgroup with a high rate of spontaneous resolution (approximately 85%) (ARRD 126:91, 1982).

Other studies have dealt with the changes produced by corticosteroid therapy on these parameters (Ga++, BAL, ACE) and overall found that Ga_{67} index usually falls and ACE and BAL lymphocytosis varies unpredictably (Baughman R.P et al ARRD 129:676, 1984; Ceuppens J.L., ARRD 129:563, 1984; Lawrence E.C. et al AJH 74:747, 1983). The study by Ceuppens is of interest since he found that although treatment with corticosteroids did not predictably change the percentage of T-lymphocytes, it appeared to reduce the T-lymphocyte helper to suppressor ratio suggesting that this may be a better way of assessing changes in these patients (ARRD 129:563, 1984). A more recent study by Hollinger suggested that the only utility of BAL in sarcoidosis is in predicting which patients will respond favorably to corticosteroid therapy. Patients with lymphocyte counts greater than 35% improved with therapy. Gallium scans and SACE levels decreased with therapy in this study but did not correlate with clinical or pulmonary function improvement (Hollinger et al ARRD 132:65-68, 1985).

Therefore, at present, the routine use of these procedures to stage patients with sarcoidosis is not recommended, though it is still a controversial issue and certainly an evolving field.

TREATMENT

There is a consensus that corticosteroids should be administered to patients with persistent hypercalcemia or with neurologic, cardiac, or ophthalmologic involvement (i.e. uveitis). The treatment of pulmonary sarcoidosis, however, still evokes a great divergence of opinion. The principal controversy is whether or not steroids have any effect on the ultimate outcome of a disease which is frequently characterized by spontaneous remissions. There are also important controversies regarding the optimal dose and duration of therapy. Many controlled studies have revealed no long term benefit from the use of steroids. These have been assailed by DeRemee (20) for design flaws, such as too low a dose of steroid, too brief a treatment period, or inclusion of inordinately high numbers of Stage I patients, i.e., patients with a high likelihood of spontaneous remission.

DeRemee also contends that once dyspnea appears, some irreversible dysfunction has occurred. He therefore treats Stage II or III patients if their chest x-ray has shown no trend toward improvement after 6 months, hoping to thwart the onset of irreversible dysfunction. However, as stated previously and as shown recently by Hillerdal et al, it may take longer than 1 year for a great number of patients to recover without treatment. Thus, there is no clear cut arbitrary time period for observation without treatment. Close (q2-3 months) follow-up of the patients with serial pulmonary function studies and symptom review is generally accepted. When therapy is indicated, corticosteroids are usually given in relatively high doses for 3-4 months and then tapered off over a period of 1 year. Steroids have been shown to be effective when given on an alternate day fashion in patients with Stage II disease (Spratling et al Chest 88(5):687, 1985). Unfortunately, there appears to be a high incidence of disease relapse when corticosteroids are tapered in either regimen. Gallium scanning and serial bronchoalveolar lavage are felt by some (5)(Keogh et al ARRD 128:256, 1983) to be the most sensitive indicators of progressive alveolitis. However, as previously discussed, this data is still preliminary and controversial.

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Other therapeutic agents have been used, including chloroquine, hydroxychloroquine, chlorambucil, Cytoxan, methotrexate, D-penicillamine, spironolactone, and allopurinol (2). Reports are anecdotal and these agents have not been consistently shown to be efficacious with the exception of hydroxychloroquine, which appears to be of benefit in patients with ocular sarcoid.

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OCCUPATIONAL LUNG DISEASE

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INTRODUCTION

Frequently physicians must investigate pulmonary complaints that may be related to a specific occupational exposure. Brooks estimates that job related respiratory diseases account for at least 65,000 acute and chronic disabilities and 25,000 deaths each year (6). The ease of diagnosis of occupational lung disease varies with the patient, the situation, and the agent inducing disease. The lung parenchyma has a limited number of responses to noxious agents, so that many different agents may produce one common pathologic state. If occupational lung disease is suspected, a detailed exposure history including the patient's occupation, location, and vocation is the most important part of the evaluation. Its value cannot be overemphasized.

Agents causing occupational lung diseases are usually classified as follows (6): (a) pneumoconioses/inorganic (mineral) dusts, (b) immunologic/pharmacologic agents, (c) irritant gases, fumes, and smoke, and (d) lung carcinogens. Only the first three classifications will be reviewed.

PNEUMOCONIOSES/INORGANIC (MINERAL) DUSTS

In 1954 Abrams defined a pneumoconiosis as "a diagnosable disease produced by inhalation of dust, dust being understood to be particulate matter in the solid phase, excluding living organisms" (1). A particle size of 0.3 to 3 microns is essential for material to reach the terminal bronchiole and alveolus(1). Larger particles are trapped in the upper airway; smaller particles do not remain in the lung. Development of clinical disease also depends on particle configuration, the intensity and duration of exposure, inherent toxicity of the material, and (probably) on the genetic background of the patient. Diagnosis is complicated by a prolonged time lag between exposure and onset of symptoms in many of the pneumoconioses, and by the widespread prevalence of other coincidental lung diseases such as bronchitis and emphysema. Typical pneumoconioses include those associated with coal dust, silica, asbestos, silver, tin, barium, iron, beryllium, tungsten, and aluminum. Diagnosis and management are similar for all the pneumoconioses. Silicosis and asbestosis are prototypical and will be discussed.

1. Silicosis

Silicosis is the most frequently encountered pneumoconiosis (1,3,6). Inhaled silicon dioxide particles are retained in the alveolus and ingested by macrophages. Macrophages transport the particles into the interstitial region and the regional lymphatics. Subsequent macrophage lysis releases lysosomes and results in activation of fibroblasts and production of intense fibrosis.

A diffuse micronodular pattern is often the first chest x-ray change seen in silicosis. Patients with this abnormality have been labeled as having "simple" silicosis; many are asymptomatic. The typical chest x-ray in "symptomatic" silicosis shows interstitial fibrosis with fibrotic nodules. These changes may progress to intense fibrotic masses with pleural thickening, local emphysema, and hilar enlargement with calcification (3). Lesions may cavitate and mimic tuberculosis. Patients who have coalescent larger nodules are classified as having "complicated" silicosis. Infiltrates are usually more prominent in the upper segments of both upper and lower lobes. Correlation between x-ray changes and functional impairment may be poor. It is rare for the chest x-ray to become abnormal with less than 20 years of exposure.

The average duration of life after first exposure has been estimated at 40 years. Hemoptysis and chest pain are common. Weight loss is typical. Nocardiosis, cryptococcosis, and sporotrichosis have been reported to complicate silicosis. Some patients with an increased particle dose for a period of 5 to 15 years will develop a syndrome of "accelerated" silicosis. The features are similar to chronic disease, but the x-ray becomes abnormal within 4 to 8 years of first dust exposure. Deterioration is rapid. Mycobacteriosis affects one-fourth of these patients, with one-half of the infections being atypical. "Acute" silicosis is a rare condition related to heavy exposure in enclosed spaces with minimal patient protection. Clinical features appear within one to three years, and most patients have a rapid downhill course. Most patients do not live long enough to develop the nodular or massive fibrotic changes on x-ray seen in the typical chronic "complicated" silicosis.

Silicosis can usually be diagnosed on history and chest x-ray alone. A history of significant exposure to free silica is required. In "simple" silicosis, pulmonary function testing results usually are normal (3). The rare symptomatic patient may have a restrictive, obstructive, or mixed pattern of impairment. Patients with "complicated" silicosis usually have abnormal diffusion capacity and exercise induced hypoxemia. Pre-terminal patients usually have severe restriction.

There is no specific therapy for silicosis; therapy is directed at preventing complications and treating infection in patients whose silicosis is complicated by tuberculosis.

Antituberculous therapy may sterilize the sputum but radiographic changes usually progress. A positive PPD may be enough evidence for diagnosis of mycobacterial infection (3). Prolonged therapy (longer than standard anti-tuberculous regimens) may be required. Bronchodilators should be used if obstruction is present.

2. Asbestosis

Asbestosis, although less common than silicosis, has generated widespread interest because of its association with bronchogenic carcinoma and malignant mesothelioma (1,2,4,5). Asbestos is a fibrosilicate of magnesium and iron. Because of its insulating and fire resistant properties it has been used extensively in ship building, fireproofing, and industrial applications. Ninety percent of the asbestos used in the United States is chrysotile (white asbestos). Crocidolite (blue asbestos) and amosite (brown asbestos) are found in South Africa. Particles of asbestos larger than 5 microns are deposited in the nose and major airways. Deposition of particles less than 1 micron in diameter occurs mainly in the peripheral airways and air spaces. Asbestos deposited in the lung may remain uncoated or be coated by a complex protein, thus forming an asbestos body (ferruginous body).

Exposure to asbestos may produce pleural disease, parenchymal disease, or both. The term "asbestosis", properly applied, denotes pulmonary fibrosis associated with asbestos exposure. However it has also been used as a general term for any of the abnormalities associated with asbestos exposure. Pleural plaques, which usually do not appear before 20 or more years after exposure, are pleural thickenings, sometimes calcified, usually located on the diaphragm or posterior lateral chest wall. They are usually bilateral but not symmetric. Patients with plaques but no parenchymal disease are usually asymptomatic. Pleural plaques are not pre-malignant. Asbestos "pleurisy" with production of pleural effusion has been described. Pulmonary fibrosis has been seen following exposure to all forms of asbestos. Crocidolite and amosite are more potent inducers of fibrosis than is chrysotile. There is a dose-effect relationship in the production of fibrosis. Small exposure over many years has the same impact as brief intense exposure.

Most patients with asbestos-related parenchymal disease present with cough and dyspnea on exertion. The chest x-ray typically shows linear irregular opacities, principally in the lower lobes. Kerley-B lines may be present. Large opacities are rare. Pulmonary function tests usually show restrictive physiology. Patients who have obstructive physiology usually are cigarette smokers. Diagnosis of asbestosis requires a history of exposure, typical chest x-ray changes, and abnormal pulmonary function tests. However, asbestos is ubiquitous in modern life, and a brief, often forgotten, exposure is all that is required to develop lung disease. There is no effective treatment for asbestosis. Treatment of coexistent lung disease and infection is indicated to maximize lung function.

Malignant mesothelioma is an uncommon and usually fatal neoplasm of the serosa of the pleural or peritoneal cavity. Most patients present with progressive chest or shoulder pain and a history of asbestos exposure. Clubbing and hypertrophic osteoarthropathy may be seen. The chest x-ray typically shows a pleural based lobulated mass. Associated effusions are common. Differentiation of malignant mesothelioma from benign pleural plaques associated with asbestos exposure may be difficult. Needle biopsy is positive in only 25% of cases (4). Cytopathology of effusions is even less rewarding. Thoracotomy is usually required for diagnosis. Progressive or symptomatic pleural disease in patients with asbestos exposure suggests mesothelioma. Radical surgery may be attempted in selected cases, but there are few long-term survivors.

Patients exposed to asbestos have an increased risk for developing bronchogenic carcinoma compared to background populations. Tumors are more common in the lower lobes than in the upper lobes and tend to be peripherally located and to involve pleura. Adenocarcinoma is the most common cell type (4). Therapy for asbestos-related bronchogenic carcinoma is the same as for typical bronchogenic carcinoma. Tobacco use interacts synergistically with asbestos, producing a phenomenal rate of lung cancer.

IMMUNOLOGIC/PHARMACOLOGIC LUNG DISEASE

1. Hypersensitivity pneumonitis

Hypersensitivity pneumonitis (extrinsic allergic alveolitis) is an allergic lung disorder resulting from sensitization to antigen following recurrent exposure to inhaled organic dust (7). The most common agents are thermophilic bacteria of the genus Thermoactinomyces. Other antigens include various fungi and avian proteins. Syndromes of hypersensitivity pneumonitis are typically labeled by either the occupation or the environmental situations in which the disease is found; i.e. farmer's lung, humidifier lung, bird fancier's disease, maple barkstripper's disease, etc. Even though organic antigens are ubiquitous, it is unusual to become sensitized without a very large antigenic exposure. Only 10 to 60% of people in a group with similar environmental exposures will become sensitized to an antigen, and only one out of three of these patients will acquire hypersensitivity pneumonitis (7). Table 1 lists some common agents associated with hypersensitivity pneumonitis.

The antigens involved cause disease by several pathways (7,8): (a) nonspecific activation of serum proteins (alternate pathway); (b) activation of alveolar macrophages; (c) immune response enhancement via a nonspecific adjuvant effect; (d) serum antibody and lymphokine production; and 3) tissue destruction via macrophage lysosome enzyme release. There is evidence for a genetically determined susceptibility to hypersensitivity pneumonitis. Although a Type III immune complex-induced entity has traditionally been used to explain the pathogenesis of hypersensitivity pneumonitis, new evidence supports an additional Type IV reaction.

Most patients present with cough, fever, chills, malaise, and dyspnea four to eight hours after exposure (7,8). Wheezing is not common; indeed, patients may have no respiratory symptoms at all, presenting with fever and malaise. Symptoms usually last 12 to 24 hours with gradual improvement if there is no re-exposure. Exposure to a low dose of antigen over a long period of time may cause a chronic form of hypersensitivity pneumonitis to develop, characterized by loss of weight and progressive dyspnea, with occasional development of pulmonary fibrosis.

The characteristic x-ray pattern for hypersensitivity pneumonitis is a diffuse miliary pattern composed of discrete, sharply defined punctate lesions. However, in the acutely symptomatic patient the chest film may be normal. The miliary pattern, if present, may coalesce into a ground-glass appearance. Confluent opacities may appear in the lower lobes. With extremely large antigen exposure, the chest film shows fine or coarse linear opacities which may progress to fibrosis and contraction, particularly in the upper lobes.

The diagnosis of hypersensitivity pneumonitis theoretically could be supported by positive skin reaction to antigen testing. However, suitable antigen is available only for bird fancier's disease, since thermophilic actinomyces are too irritating to be injected into the skin. Precipitating serum antibodies are commonly found in many of the syndromes of hypersensitivity pneumonitis. Positive precipitins coupled with a history of exposure with subsequent development of disease establishes the diagnosis. Lung biopsy may show interstitial granulomatous pneumonitis, but is not usually necessary for diagnosis.

Therapy consists of avoiding further exposure. Acutely, treatment with steroids may produce more rapid symptomatic improvement. Fibrosis from long-standing exposure is usually irreversible.

2. Occupational Asthma

IgE-mediated asthma is seen with exposure to organic material such as castor bean, animal dander, and serum proteins. Non-IgE-mediated or pharmacologic mechanisms seem to cause the bronchospasm associated with toluene diisocyanate and western red cedar exposure. Many other chemicals are associated with development of acute bronchospasm following exposure. The acute bronchospasm in these syndromes is treated by standard asthma therapy. Identification and avoidance of the inciting agent is required to prevent significant recurrences of bronchospasm. Inhalational challenge testing has been used for diagnosis of bronchospasm induced by a wide variety of chemicals but is potentially hazardous and should be performed only by experienced personnel.

LUNG DISEASE FROM IRRITANT GASES, FUMES, SMOKES

These agents cause injury through asphyxiation, systemic toxicity, immunologically mediated responses, or mucosal and alveolar damage. The most common sources of irritant gas exposure are fires. Common chemical gases include chlorine, phosgene, ammonia, sulfur dioxide, and oxides of nitrogen. Conducting airway injury may manifest itself as upper airway obstruction, laryngotracheitis, and bronchitis. Peripheral airway obstruction is caused by bronchiolitis from marked airway edema and hypersecretion. Air flow obstruction may be due to desquamation or increased secretions and reflex bronchospasm from irritation. A typical clinical presentation is one of acute respiratory distress syndrome presenting with restrictive physiology, profound V/Q mismatch and shunting. Therapy for exposure to toxic gases is supportive. Intubation may be difficult because of oropharyngeal injury. There are no controlled studies regarding the clinical use of steroids in patients with noxious gas lung injury. The use of prophylactic antibiotics has not been critically evaluated. Bronchodilators are of use in treating airways obstruction. Ventilator support with PEEP may be required. The prognosis of patients who survive the acute injury induced by inhalation of toxic gases is usually good. Permanent residual functional impairment is unusual. However, permanent restrictive defects have been seen with oxides of nitrogen, ammonia, and sulfur dioxide.

CONCLUSION

Occupational lung disease is prevalent in industrial societies. Most syndromes begin with obscure symptoms; physiologic abnormalities usually become apparent only late in the course of the disease. The most important element in diagnosis is a history of exposure; the most important element in treatment is removal from the offending environment (6).

TABLE I
(Adapted from Reference 7)

Some Etiologic Agents Associated with Hypersensitivity Pneumonitis

Disease	Exposure	Specific Inhalation
Farmer's lung	Moldy hay and other fodder	Micropolyspora faeni; Thermoactinomyces vulgaris
Bagassosis	Moldy sugar cane	Thermoactinomyces vulgaris
Mushroom worker's disease	Mushroom compost	Micropolyspora faeni; Thermoactinomyces vulgaris
Humidifier lung	Contaminated system	Thermophilic actinomycetes; other?
Air Conditioner lung	Contaminated system	Thermophilic actinomycetes; other?
Malt worker's disease	Moldy malt	Aspergillus clavatus; Aspergillus fumigatus
Bird fancier's disease	Pigeon, budgerigar, parrot, hen, turkey droppings	Avian serum proteins
Maple bark stripper's disease	Moldy maple logs	Cryptostroma corticale
Cheesewasher's disease	Cheese mold	Penicillium caseii
Furrier's lung	Hair dust	Animal proteins?

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THE ADULT RESPIRATORY DISTRESS SYNDROME

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HISTORY

The Adult Respiratory Distress Syndrome (ARDS) is characterized by dyspnea, hypoxemia, decreased pulmonary compliance and diffuse bilateral pulmonary infiltrates. It commonly occurs following a catastrophic event in individuals with no previous lung disease (1-2). The term ARDS was coined in 1967 by Ashbaugh, Bigelow and Petty, who also defined criteria for making its diagnosis (Table 1) (1,2) The exact incidence of ARDS is not known but is estimated at 150,000 cases per year in the USA.

Table 1 CRITERIA FOR DIAGNOSING THE ADULT RESPIRATORY DISTRESS SYNDROME

A. Clinical Setting
    1. Catastrophic event
        a. Pulmonary
        b. Nonpulmonary, e.g., shock
    2. Exclusions
        a. Chronic Pulmonary Disease
        b. Left heart abnormalities
    3. Respiratory distress (judged clinically)
        a. Tachypnea > 20, usually greater
        b. Labored breathing
B. X-ray: Diffuse Pulmonary Infiltrates
    1. Interstitial (initially)
    2. Alveolar (later)
C. Physiologic
    1. PaO2 < 50 with FiO2 > 0.6
    2. Overall compliance < 50 cc/cm H2O-usually 20-30 cc/cm H2O
    3. Increased shunt fraction Qs/Qt and deadspace ventilation Vd/Vt
D. Pathologic
    1. Heavy lungs, usually > 1000 gm
    2. Congestive atelectasis
    3. Hyaline membranes
    4. Fibrosis

Although this term is relatively new, physicians have been describing for many years the adverse pulmonary effects of both thoracic and extra-thoracic trauma as well as other types of catastrophic illness. Traumatic lung injuries in World War I were usually fatal, but improved resuscitation therapy in World War II resulted in increased casualty survival and subsequently an increase in a phenomenon then called "traumatic wet lung" (3-

4). In the 1950's and the 1960's numerous reports of the same clinicopathologic condition appeared in the literature. Each new author that described the syndrome also renamed it, causing an enormous amount of confusion (Table 2) (5-6). During the Vietnam war excellent early resuscitation and field evacuation created large numbers of combat casualties who survived the initial phases of care only to succumb to ARDS (8).

Table 2 SYNONYMS FOR ARDS

Adult Hyaline Membrane Disease
Adult Resp. Insufficiency Syndrome
Congestive Atelectasis
DaNang Lung
Hemorrhagic Atelectasis
Hemorrhagic Lung Syndrome
Hypoxic Hyperventilation
Post Perfusion Lung
Post Traumatic Atelectasis
Post Traumatic Pulmonary Insufficiency
Progressive Pulmonary Consolidation
Progressive Respiratory Distress
Pump Lung
Shock Lung
Traumatic Wet Lung
Transplant Lung
White Lung
Wet Lung

The usefulness of lumping together all forms of acute lung injury under the title ARDS has been hotly debated in the past decade as evidenced by editorials by Fishman and Murray (9,10). The term does create a useful conceptual framework upon which to base integrated systematic therapy and at least for the immediate future is here to stay.

PATHOPHYSIOLOGY

In spite of the numerous etiologies of this syndrome, the clinicopathological outcome is often the same. It is not clear, however, whether the mechanisms of lung injury are similar in all cases. Most of the data relating to the pathogenesis of acute lung injury in the adult come from animal experimentation and can therefore only be extrapolated to humans with caution. Structural and functional injuries coexist in this disorder. Whether the initial injury is one of structure or function is not clear. For years it was assumed that all of the functional abnormalities were secondary to the structural changes. This notion has never been proven and, in fact, may not be true (11).

The lung's structural response to insult and subsequent attempted repair can be divided into an exudative phase, an early proliferative phase and a late proliferative phase (Table 3) (12).

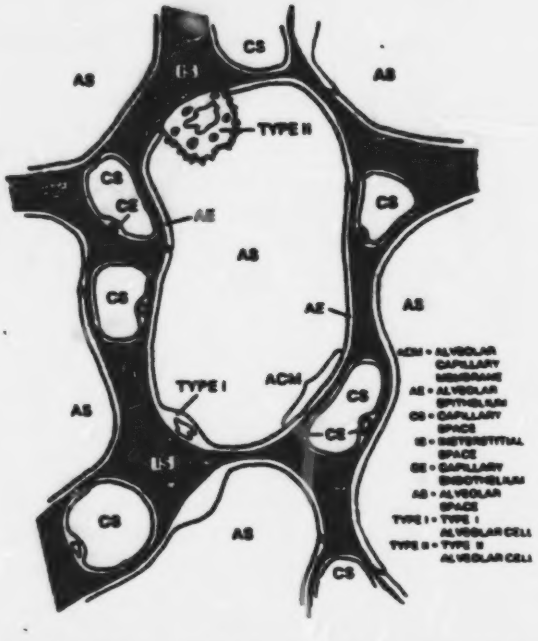
Table 3. STRUCTURAL RESPONSE TO INJURY

Exudative Phase (24-96 hours)
  Alveolar and interstitial edema
  Capillary congestion
  Destruction of type I alveolar cells
  Early hyaline membrane formation

Early Proliferative Phase (3-10 days)
  Increased type II alveolar cells
  Cellular infiltration of the alveolar septum
  Organization of hyaline membranes

Late Proliferative Phase (>7-10 days)
  Fibrosis of hyaline membranes and alveolar septum
  Alveolar duct fibrosis

In the normal alveolus gas is separated from the capillary blood by the thin alveolar-capillary membrane (Fig 1). Type I alveolar cells cover 95% of the alveolar surface area and type II alveolar cells cover the remaining 5%.



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ACM = ALVEOLAR CAPILLARY MEMBRANE
AE = ALVEOLAR EPITHELIUM
CS = CAPILLARY SPACE
IS = INTERSTITIAL SPACE
CE = CAPILLARY ENDOTHELIUM
AS = ALVEOLAR SPACE
TYPE I = TYPE I ALVEOLAR CELL
TYPE II = TYPE II ALVEOLAR CELL

Fig. 1. The alveolar epithelium is composed of type I and type II alveolar cells, but most of the alveolar surface area is covered by the cytoplasm of type I cells. This drawing depicts the close relationship of the capillary endothelium to the alveolar epithelium at the alveolar capillary membrane where gas exchange occurs. The interstitial space seperates the alveolar epithelium from the capillary endothelium. The thickness of the interstitial space is exaggerated.

The alveolar capillaries travel in close proximity to the alveolus. Both alveolar epithelium and capillary endothelium rest upon basement membranes. The interstitial space lies between the two membranes and contains fibrous connective tissue, interstitial fluid and an occasional fibroblast. These membranes fuse at the capillary-alveolar interface forming a membrane with a thickness of about 0.5 microns and allow efficient gas exchange.

Within 24 hours of injury, alveolar and interstitial edema develop. The alveolar septum is thickened. Erythrocytes and inflammatory cells begin to move into the interstitium and alveolus. Type I alveolar cells are destroyed leaving denuded basement membrane. While type I alveolar cells are quite sensitive to injury, type II alveolar cells are more resistant. The alveolar epithelial damage appears to be much more severe than the damage to the capillary endothelium (Fig 2) (13).

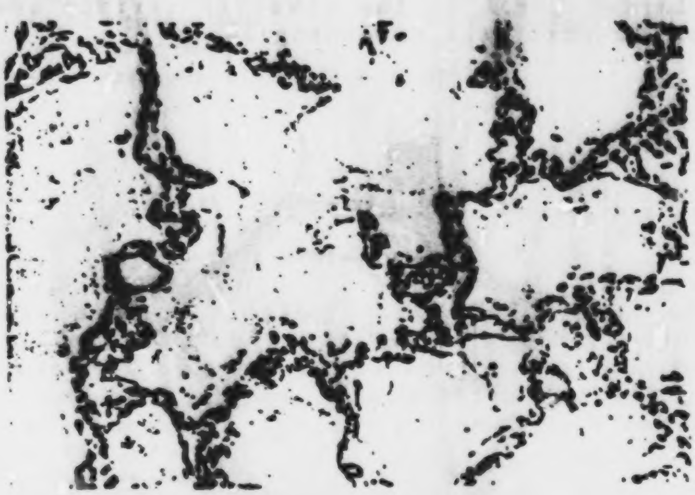

Fig. 2. Pulmonary edema and alveolar spaces filled with proteinaceous material are seen. The underlying alveolar walls are edematous and the capillaries are congested.

Within approximately 72 hours of injury a dramatic proliferation of type II alveolar cells occurs. These cuboidal cells may form a continuous layer covering the previously denuded basement membrane. The alveolar septum is markedly thickened and is infiltrated by proliferating fibroblasts, plasma cells, leukocytes and histiocytes. Hyaline membranes begin to organize and microatelectasis is seen. Capillary endothelial injury becomes more apparent at this stage (Fig 3) (14).

Fig. 3. Proliferation of type II alveolar cells, markedly thickened septum with cellular proliferation, and hyaline membranes are seen.

After seven to ten days fibrotic changes begin to take place both in the alveolar septa and in the hyaline membranes. The alveolar structure is no longer recognizable. The fibrosis is most apparent in the respiratory ducts and bronchioles (Fig 4). Fibrin and platelet microemboli are often found within the lumina of the capillaries. Capillary injury, however, may occur with little morphologic change in the endothelial cells.

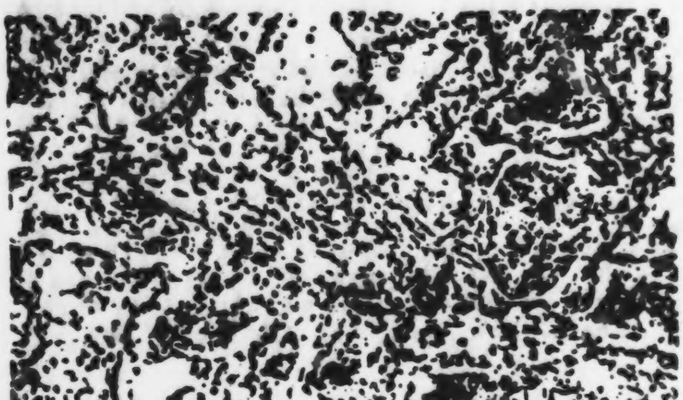

Fig. 4. The pulmonary architecture is markedly distorted. The alveolar spaces are almost obliterated and the alveolar septa are markedly thickened.

NON-CARDIAC PULMONARY EDEMA

Non-cardiogenic pulmonary edema is a central feature of ARDS. Staub and co-workers using a sheep model of ARDS have demonstrated convincingly that this increase in lung water is secondary to a derangement of alveolar-capillary permeability (15,16). Under normal circumstances a small amount of fluid moves across the endothelial membrane into the interstitial space. The fluid then moves quickly into the peribronchiolar or pleural lymphatics and then out of the lung. This lung lymph flow is approximately 10-20 cc per hour. The type I alveolar cells which make up most of the alveolar surface area are joined by tight intercellular junctions. This epithelial membrane is almost impermeable to water, solute and protein. The capillary endothelial cells on the other hand have very loose intercellular junctions which allow the passage of water and solutes but generally are impermeable to protein (Fig 5).

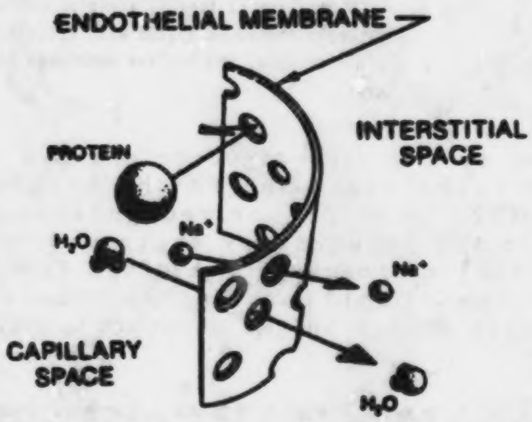

Fig. 5. The intact endothelial membrane is permeable to water and solutes but impermeable to protein.

The movement of water across this membrane is determined by the balance of hydrostatic and osmotic pressures which oppose one another across the membrane. Realising these principles Ernest Starling developed the equation for net fluid filtration over eighty years ago (Fig 6) (17).

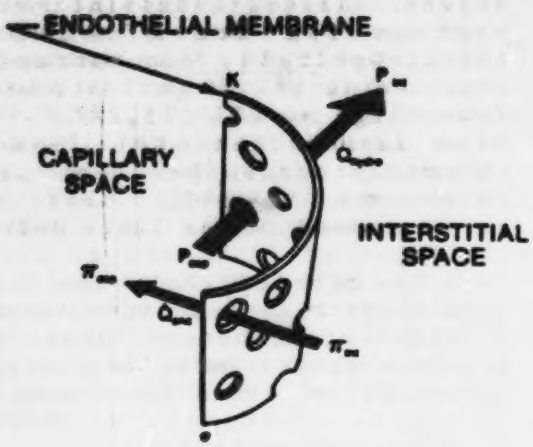

Fig 6. The total fluid filtration across the endothelial membrane into the interstitial space is the sum of the fluid filtration generated by the hydrostatic pressure gradient which tends to move fluid into the interstitial space and the filtration generated by the oncotic pressure gradiant which tends to pull fluid into the capillary space.

THE STARLING EQUATION

$$\dot{Q}_f = K(P_{cap} - P_{int}) - K\sigma(\pi_{cap} - \pi_{int})$$

A disruption of the alveolar-capillary membrane follows acute lung injury regardless of the etiology. This disruption causes an increased permeability which allows filtration of fluid and protein into the interstitial space and alveoli at relatively low hydrostatic pressures.

HUMORAL MEDIATORS OF ARDS

In recent years both experimental and clinical evidence has accumulated to implicate neutrophil aggregation, stasis, and chemotaxis in pulmonary capillaries as major contributors to the initial pulmonary endothelial injury (18,19,20). The major leukocyte aggregants are C5a and its metabolites. Other factors which are directly chemotactic or which may exert their effect by activating C_5 include platelet activating factor, leukotriene B_4, and thromboxane A_2. Which of these (or other undiscovered factors) is the initiating factor remains to be proven(46). Neutrophils are capable of both endothelial and interstitial damage. They release superoxide radicals and other highly reactive oxidants which injure endothelial cells. Polymorphonuclear granulocytes also release neutral and acid proteases that destroy collagen, elastin and fibronectin. In addition these proteases cleave fibrinogen, Hageman factor and complement. The neutrophil proteases not only destroy structural proteins but also amplify the inflammatory response via complement activation which results in further lung injury. Normal lung defense mechanisms that protect against proteolytic damage (alpha-1 antitrypsin) have been shown to be inactivated by the superoxide radical and oxygen.

Other factors are involved in acute pulmonary endothelial injury. Disseminated intravascular coagulation and platelet aggregation are often found in patients with ARDS. Angiographically demonstrated pulmonary thrombosis has been observed in 48% of patients with ARDS, and DIC has been reported in as high as 23% (21,22). Thrombocytopenia is often present even if DIC cannot be demonstrated. In septic patients, thrombocytopenia has been associated with increased risk of subsequent ARDS (41). Platelets have a reduced half-life and are deposited in the lungs and reticuloendothelial system.

The fibrin/fibrinogen degradation product "D-antigen" has been found to be elevated in patients with ARDS. It seems to be a marker of pulmonary microvascular injury. Fibrin degradation products are known to be capable of altering alveolar-capillary permeability. When the D-monomer is infused into dogs it causes tachypnea, tachycardia, hypoxemia and increased alveolar capillary permeability.

Little is known of the role of prostaglandins in human lung injury. However prostaglandins in concert with capillary obstruction by leukocyte, platelet, and fibrin thrombi help mediate pulmonary artery vasoconstriction and hypertension (23). Early studies of leukotriene C_4 and D_4 have documented their ability to increase vascular permeability. However, assays are not yet sensitive enough to study changes in levels in ARDS (46).

Abnormality in surfactant function has been clearly demonstrated in this syndrome. Loss of this effective surface active agent causes collapse of alveoli with an attendant decrease in FRC and reduced pulmonary compliance. In the infant respiratory distress syndrome there is a primary surfactant abnormality which is central to the pathogenesis. In contrast, the surfactant abnormality in ARDS is not a primary event but rather a later complication following acute lung injury (27,28).

The major pathologic sequela of ARDS is a by-product of the lung's reparative response to injury, namely pulmonary fibrosis. A link between the "capillary leak" syndrome and a disordered fibrotic response has never been demonstrated. Several possibilities exist. Endotoxinemia may, for example, stimulate connective tissue synthesis directly. Alveolar macrophages or activated lymphocytes may stimulate fibroblast proliferation. Acutely injured endothelial cells may cause tonic inhibition of fibroblast proliferation to subside. It is also possible that therapeutic manipulations such as positive pressure ventilation with positive end expiratory pressure, oxygen therapy, platelet infusions and others may augment or modify the lung's reparative response. Changes in lung mechanics are typical of ARDS. Specifically, there is a decrease in functional residual capacity (FRC) and a decrease in lung compliance. Increased lung water may explain these changes late in ARDS; however, there are animal data showing that alteration in airway function occurs prior to the development of pulmonary edema. It has been demonstrated that, following injection of *E. coli* endotoxin, there is a fall in lung compliance and in FRC prior to the development of pulmonary edema (24,25). At least in animal models prostaglandins are involved, as pretreatment with cyclooxygenase inhibitors has completely blocked the hypoxemia, increased airways resistance and initial pulmonary hypertension normally seen with endotoxin infusion (50). Before using these drugs in patients, careful clinical studies will be required, especially in view of their potential detrimental effects on poorly perfused kidneys. Endotoxin has also been demonstrated to prevent hypoxic pulmonary vasoconstriction. These functional changes serve to increase ventilation-perfusion mismatching and intrapulmonary shunting and are in part responsible for the early severe hypoxemia seen in this disorder.

CLINICAL AND PHYSIOLOGIC COURSE OF ARDS (56)

ARDS starts with an injury to the lung from any of the disease etiologies listed (see Table 4). The patient may seem to recover from the acute insult with stability of his respiratory and circulatory systems restored. However, after a latent period of several hours to seven days, respiratory difficulty ensues.

Table 4. Conditions Associated with the Adult Respiratory Distress Syndrome

- Shock
  - Hemmorrhagic
  - Septic
  - Cardiogenic
  - Anaphylactic
- Trauma
  - Fat emboli
  - Lung contusion
  - Non-thoracic trauma (especially head trauma)
- Infection
  - Viral pneumonia
  - Bacterial pneumonia
  - Fungal pneumonia
- Inhalation of Toxic Gases
  - Oxygen (FiO2 > 0.5)
  - Smoke
  - Nitrous oxide
- Aspiration of Gastric Contents (especially with a pH <2.5)
- Drug Overdose
  - Heroin
  - Methadone
  - Barbiturates
  - Ethchlorvynol
- Disseminated Intravascular Coag.
- Near-Drowning
  - Fresh or salt water
- Miscellaneous
  - Pancreatitis
  - Uremia
  - Post cardiopulmonary bypass
  - Post cardioversion
  - Multiple transfusions
  - Air or amniotic fluid emboli

Tachypnea is an early manifestation. With increasing severity of ARDS, the patient develops progressive dyspnea and rapid (greater than 35 per minute) shallow respirations. Rales are heard and tachycardia is expected. Cyanosis is present in severe cases.

The arterial oxygen tension drops and the alveolar-arterial oxygen gradient, A-a DO_2, widens early in the disease. The widened A-a gradient may not correct completely with 100% inspired O_2, indicating the presence of shunt physiology. With progression, even FIO_2 equal to 1.0 may not satisfactorily oxygenate the patient, and the shunt may reach 50 to 60%.

A large shunt, characteristic of ARDS, is caused by perfusion of atelectatic areas of the lung. The PCO_2 remains low throughout most of the course; if elevated it is an especially bad prognostic sign.

The chest x-ray shows an interstitial or reticular infiltrate which spreads rapidly throughout the lung. It quickly assumes an alveolar pattern and may be most prominent peripherally.

Spirometry is compatible with a restrictive defect, showing low FVC (<15 ml per kg) and low tidal volumes (<5 ml per kg). Lung volumes confirm the restrictive (not obstructive) physiology, showing greatly reduced FRC and TLC. Dead space to tidal volume ratio is often greater than 0.6 (normal <0.35). If a compliance measurement is made (typically done with an "inflation hold" maneuver with the patient on a ventilator) the lung and thoracic cage are found to be poorly compliant or "stiff", another hallmark of ARDS.

A Swan-Ganz catheter may be necessary to differentiate ARDS from cardiogenic edema. Expected findings include: normal PCW (less than 12mm Hg), slightly increased PA pressures initially, and normal to high cardiac output. With increasing severity, pulmonary hypertension develops due to increased pulmonary vascular resistance, and pre-terminally there may be marked pulmonary hypertension and falling cardiac output. Differentiation of noncardiac pulmonary edema (ARDS) from cardiac edema can be difficult. However, many of the clinical, historical, laboratory, hemodynamic, and radiographic findings which aid in the diagnosis are summarized in Table 5. These are general guidelines and exceptions do occur.

Table 5 – Initial Differentiation of CPE from NCPE (ARDS)

CLINICAL PRESENTATION
- Respiratory distress
($\uparrow$ RR; $\downarrow$ PaO_2, $\downarrow$ $PaCO_2$)

	Cardiac Pulmonary Edema	Noncardiac Pulmonary Edema
HISTORY	• Acute Cardiac Event	• Acute cardiac event is uncommon in immediate history (but possible!) • Underlying disease? (Table 4)
CLINICAL EXAMINATION	• Low flow state = cool periphery • S_3 gallop/cardiomegaly • Jugular venous distention • Crackles (wet)	• Usually high flow state = warm periphery • Bounding pulses • No gallop • No jugular venous distention • Crackles (dry) • Evidence of underlying disease (eg, peritonitis)
LABORATORY	• ECG, ischemia/infarct? • CXR, peri-hilar distribution, possible cardiomegaly • Cardiac enzymes may be $\uparrow$ • PCWP >18 mm Hg • $\dot{Q}s/\dot{Q}t$—small $\uparrow$ • Edema fluid/serum protein <.5	• ECG, usually normal • CXR, peripheral distribution • Cardiac enzymes usually normal • PCWP <18 mm Hg (unless fluid loaded with resuscitation) • $\dot{Q}s/\dot{Q}t$—large $\uparrow\uparrow$ • Edema fluid/serum protein <.7

In summary, the essential clinical aspects of ARDS include: dyspnea, chest x-ray infiltrates, large shunt causing low FaO_2, non-compliant lungs, and reduced lung volumes, especially FRC.

TREATMENT

Despite the varied etiologies the derangement of pulmonary physiology in ARDS is treated in basically the same way regardless of the inciting cause. It is essential to search for the underlying cause, however, so that specific therapy may be directed towards it. Management requires the support of all systems and correction of the underlying etiology for the ARDS (whenever possible), while allowing the lung time to recover from the acute insult. It is not expected that any respiratory therapy maneuvers will accelerate the healing process in the lung. Rather, the goals of respiratory therapy are adequate tissue oxygenation and CO_2 elimination via intubation and carefully monitored mechanical ventilation, using supplemental oxygen and PEEP. The details of ventilator support are covered elsewhere but a few comments will be made here:

1. The decision to intubate is usually made when a $PaO_2 \geq 60$mm Hg cannot be achieved via mask oxygen in the patient with ARDS. Physiologic measurements are helpful, and factors favoring mechanical ventilation include (6):

   a. $PO_2 \leq 60$ on $FiO_2 = 1.0$

   b. A-a $DO_2 > 400$ on $FiO_2 = 1.0$

   c. Shunt greater than 30%

   d. Vital capacity less than 15 ml per kg.

   e. V_D/V_T greater than 0.6

2. Nasotracheal intubation is preferred unless tenacious secretions are a problem (57). Use of a large volume, low pressure "floppy" cuff minimizes tracheal damage. The new low pressure cuffs may be kept in place at least 3 weeks before tracheostomy is considered (58).

3. Some suggested initial ventilator settings include:

   a. Tidal volume - 10-15 ml per kg (use lower range in COPD)

   b. Respiratory rate - 10-14 per minute

   c. FiO_2 - 1.0

   d. PEEP - 5 cm H_2O

   e. Assist-control or IMV (See chapter on mechanical ventilation for pros and cons)

Adjustments are then made using frequent measurement of arterial blood gases (initial reading in 20 minutes).

TABLE 6
USEFUL FORMULAE FOR ARDS

1. Physiologic dead space $\frac{V_D}{V_T} = \frac{P_aCO_2 - P_ECO_2}{P_aCO_2}$ (Normally ≤ 0.35)

Where P_ECO_2 is the partial pressure of CO_2 in a collection of mixed expired gas. Such a collection can easily be done on control, assist, or SIMV modes (eg BEAR-1), but not on constant flow IMV mode on the MA-1.

2. Oxygen content = Hgb (gm%) X (% saturation) x 1.39

$+ 0.003 \times PO_2$

3. Shunt $\frac{Q_s}{Q_t} = \frac{CcO_2 - CaO_2}{CcO_2 - C\bar{v}O_2}$ (Normally $\leq$ 0.05)

Where CcO_2 = Capillary O_2 content (calculated using P_AO_2 from the alveolar air equation)

CaO_2 = Arterial O_2 content

$C\bar{v}O_2$ = Mixed venous O_2 content (from distal port of S-G catheter)

4. Some hemodynamic normal values:

a. Pressures (in mmHg)

CVP = 0 - 8

RA = 0 - 6

RV = 15 - 30 / 0 - 5

PA = 15 - 30 / 5 - 14

PCW = 5 - 12; and normally (PA diastolic) - (PCW) $\leq$ 5

b. Resistance (in dyne sec cm^{-5}):

$$PVR = \frac{(\text{PA mean pressure} - \text{PCW})}{\text{C.O.}} \times 80 = 80 - 200$$

$$SVR = \frac{(\text{Aortic mean pressure} - \text{RA pressure})}{\text{C.O.}} \times 80 = 800 - 1300$$

c. Flow

$$CI = \frac{CO}{BSA} = 2.5\text{-}4.5 \text{ L/min/ } M^2$$

5. Lungs and chest wall compliance =

$$\frac{\text{Tidal Volume} - \text{Tubing Expansion Volume}}{\text{Peak Airway Pressure} - \text{PEEP}}$$

Normal static compliance $>$ 80 cc/cm H_2O

Tubing expansion volume = (3cc) x (Peak airway pressure - PEEP)

6. Other values:

$CaO_2 - C\bar{v}O_2 \leq 5$ vol%

$P\bar{v}O_2 \geq 35$ mm Hg

4. PEEP (Positive End Expiratory Pressure) is the mainstay of treatment. PEEP allows adequate oxygenation of the patient without high FiO_2 while the lungs recover. It does not reduce total lung water or accelerate the healing process(es). The apparent improvement seen on chest x-ray after institution of PEEP is due to an increase in the volume of air-filled lung. PEEP works mainly by raising FRC, which is severely reduced in ARDS, and recruiting unstable alveoli which would otherwise close (40). Thus, PEEP decreases intrapulmonary shunt. The level of PEEP to use is controversial, but a reasonable goal is to use the minimum amount of PEEP required to achieve the following (40):

a. $PaO_2 > 60$ with $FiO_2 \leq .50$

b. Reasonable tissue oxygenation (as determined by mixed venous blood gases, urine output, mental status, blood pH, and O_2 delivery).

c. Acceptable blood presure and cardiac output. Remember O_2 delivery is the final assessment of overall cardiorespiratory function.

PEEP should be instituted at 5 cm H_2O and increased by 5 cm increments every 20-30 minutes until acceptable levels of monitored values are obtained (51). For further discussion see chapter on mechanical ventilation.

5. Swan-Ganz catheterization should be performed on virtually all patients with ARDS, especially if 10 cm H_2O or greater of PEEP is to be used. This allows measurements of RA, RV, PA, PCW, CO, PvO_2 and calculation of PVR, SVR, shunt, A-V O_2 difference, and various indices of O_2 delivery. Table 6 lists useful formulae commonly used in the management of critically ill patients.

6. Fluid status: It is probably best to keep the PCW in the normal range and not let the patient gain weight (57). If no nutritional support is used, expect a loss of 0.5 kg per day in weight (57). Diuretics should be used as necessary,determined by changes in respiratory and circulatory parameters. Some centers advocate keeping the patient very "dry" (to the point of using pressor drugs for blood pressure support) to avoid further fluid leaks into the lungs; there are no data to support this approach.

7. Crystalloid versus colloid: This area is still not completely settled. There is evidence (59)

that lung water may be increased by the use of colloid. Colloid is much more expensive than crystalloid; most experts now prefer crystalloid solutions for fluid replacement and resuscitation.

8. Corticosteroids: There is no evidence for the use of steroids in established ARDS (61,45). Steroids in large doses (methylprednisolone 30 mg/kg) may be beneficial in gram negative septic shock when given very early (62). However, this does not imply that they are of any use in ARDS which has resulted from septic shock. In aspiration, steroids may even be harmful, predisposing to gram negative rod pneumonia (63).

9. Nutritional support: One of the most important advances in intensive care medicine has been the recognition of nutritional needs of critically ill patients. Feeding should be started early, enterally if possible, but parenterally if necessary (52).

MAJOR COMPLICATIONS IN PATIENTS WITH ARDS

1. Pneumonia, especially gram negative rod infections. Be aggressive in antibiotic use. Superimposed pneumonia on an already markedly abnormal chest x-ray can be difficult to diagnose; suggested criteria for diagnosis are any three of the following (64): new or higher fever, leukocytosis, purulent tracheobronchial secretions, or new infiltrates. Culture of sputum from the endotracheal tube is not very useful, as these tubes are quickly colonized with gram negative rods. A positive blood culture, however, may be diagnostic if the clinical picture is compatible.

2. Barotrauma, e.g. pneumothorax: This is common with aspiration and with high peak airway pressures. It occurs most frequently at a time when the patient appears to be getting better. Pneumothoraces are usually under tension, and can rapidly lead to death if not recognized and treated. Once chest tubes are inserted, they should probably be left as long as high levels of PEEP are used. The use of prophylactic chest tubes is controversial (65).

3. Pulmonary embolism: Low dose heparin, 5000 units every twelve hours, should be used prophylactically if there is no contraindication (based on a historical control study in a respiratory ICU) (60).

4. GI Bleeding: This is possibly preventable by titrating stomach pH to greater than 3.5 with antacids (66). Ranitidine is used as well although the data on its use is unclear. Sucralfate may be preferable to reduce the risk of colonization (67).

5. A decline in cardiac output from ventilator therapy may occur and is especially likely when first initiating mechanical ventilation (40). It may be due to inadequate intravascular volume, excessive PEEP or excessively large tidal volume. IMV may preserve cardiac output better than control or assist modes when high levels of PEEP are needed. First therapy should be fluid resuscitation and inotropic agents. Lowering PEEP or lowering tidal volume may be necessary. Don't forget to check for pneumothorax as well. Excellent reviews of management, pathophysiology and current research are available (36-40, 54-55).

PROGNOSIS

The outcome depends on many factors, including the specific etiology of the ARDS. Hence, there is no "average" mortality in ARDS. Some figures given by Alan Pierce on mortality for various etiologies include (64):

Fat embolism - 10-20%

Smoke inhalation - 10-50%

Post traumatic pulmonary insufficiency - 40-60%

ARDS with septic shock - 70%

It is rare to be unable to adequately oxygenate a patient with ARDS; death usually results from the inciting injury or the complications of the illness rather than hypoxemia. The use of the extracorporeal membrane oxygenator (ECMO) was advocated in cases where even high levels of PEEP failed to achieve adequate PaO_2, but no benefit in mortality has been shown in the ECMO trial, probably due to the severe degree of illness in this group of patients (61,29). In patients dying of ARDS in the ECMO trial, severe interstitial and intra-alveolar fibrosis appeared to be a major cause of death (47). A recent study of a less skewed population (53) showed irreversible respiratory failure accounted for only 16% (5 of 32) of ARDS deaths. Eighty percent (8 of 10) of early deaths (first 72 hours) were due to presenting illness or injury. Late deaths (>72 hours) were due to sepsis (35% of deaths) followed in frequency by cardiac, respiratory, CNS and hematologic causes. Patients with ARDS were 6 times as likely to develop sepsis after onset of ARDS than control patients, usually from a pulmonary source. Clearly, the major causes of death are the underlying injury or illness and complicating sepsis or multiple organ failure.

Use of the high frequency jet ventilator, with respiratory rates to 500 per minute, is being investigated and may aid in the treatment of the patient with ARDS when its application is better understood (See chapter on mechanical ventilation).

Long-term followup of patients who have recovered from ARDS shows surprisingly infrequent permanent damage (43,49). A mild restrictive and/or obstructive ventilatory abnormality, moderate diffusion defect and normal resting arterial blood gases are the usual findings in the recovered ARDS patient studied two years after the injury. These abnormalities tend to slowly improve over time. If the severely ill patient with ARDS can be supported through the acute phase of his illness and its complications, the chance for survival with relatively normal lung function is excellent.

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VASCULAR DISEASES OF THE LUNG

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PRIMARY PULMONARY HYPERTENSION

The pulmonary circulation is designed as a high flow, low resistance circuit which can accommodate increases in cardiac output without excessive elevation of mean arterial pressure, due to the high compliance of the thin walled vessels. Pulmonary hypertension is defined as elevated pulmonary artery pressure (mean arterial pressure >25mmHg) that is sustained for a given level of blood flow. It is the final common pathway for a number of diverse clinical conditions that affect pulmonary arterial pressure through different mechanisms. Their effects on pulmonary blood flow and resistance are expressed by Poiseuille's Law:

$$\text{Resistance (R)} = \frac{\text{mean pulm art pressure (P)}}{\text{blood flow (Q)}} = \frac{8ul}{r^4}$$

where u = blood viscosity, L = length of vasculature, and
r = mean radius of vessel or vasculature

The following table relates the clinical condition to the specific mechanism for the development of pulmonary hypertension (34).

Table 1—*Mechanisms of Pulmonary Arterial Hypertension*

Mechanism	Clinical Example
Increased venous pressure	Mitral stenosis Left ventricular failure
Increased blood flow	Congenital left-to-right intracardiac shunts
Increased blood volume	Left ventricular failure
Increased blood viscosity	Polycythemia
Decreased effective radius of arterial bed	
a. Loss of vessels	After pneumonectomy
b. Vascular obstruction	Pulmonary embolism
c. Narrowing of luminal diameter	
1. Anatomic, eg, smooth muscle hypertrophy	Chronic hypoxia
2. Vasoconstriction	Primary pulmonary hypertension
Increased intrathoracic pressure	COPD

Clinically, primary pulmonary hypertension, to which this discussion will be limited, is defined by exclusion; it is pulmonary hypertension in the absence of congenital heart disease, clinically demonstrable thromboembolic disease, or significant disturbance in ventilation (COPD). Also excluded are diseases that cause post-capillary hypertension such as mitral stenosis, left atrial tumors, left ventricular dysfunction, or pulmonary veno-occlusive disease. Only the latter is a primary vascular disease of the lung; it is a rare, untreatable childhood illness that physiologically resembles chronic mitral stenosis.

Primary (unexplained) pulmonary hypertension (PPH) is an uncommon disease of young adulthood; it is probably a spectrum, rather than a single disease. In one histopathologic study of 80 patients from the Mayo Clinic (35), forty-five (56%) had thromboembolic disease (clinical misdiagnosis), and 22 (28%) had "plexogenic arteriopathy", characterized by medial hypertrophy of vessel walls, intimal proliferation of arterioles, focal fibrinoid necrosis of muscular arteries, and the development of tortuous channels separated by stroma within dilated vessels. The remaining patients (16%) had pulmonary veno-occlusive disease, primary pulmonary arteritis, or chronic pulmonary venous hypertension.

The etiology of this "disease" is unclear. There appears to be a familial form of the disease, which is autosomal dominant with variable penetrance. Although some patients with PPH have associated evidence of collagen vascular disease (Raynaud's phenomenon in 10-30%, ANA (+) in 50-80%) (36), most cases are "idiopathic". Moveover, in small series, steroids and azathioprine do not appear to be of benefit. Differentiation of PPH from chronic pulmonary thromboembolism can sometimes only be made pathologically, but there are clinical differences; most patients with PPH are younger (under 35) and have occlusion of larger arterioles (100-250um). Patients with thromboembolism are older (over 40) and have selective loss of small arterioles (<60um).

PPH is a progressive disease with an average survival of only 1-3 years after onset of symptoms, but this is widely variable. Long term survival is not uncommon, and prognosis appears to be independent of age of onset or initial pulmonary artery pressure. Impaired cardiac function (i.e. decreased stroke volume index) is the worst prognostic sign.

The majority of patients are women in their 20's and 30's who present with dyspnea on exertion. Less prevalent symptoms include dizziness, fatigue, chest pain, and palpitations. The physical exam is usually normal. Clubbing is absent; its presence should suggest secondary pulmonary hypertension. The lungs are clear to auscultation. If fine rales are heard, diffuse interstitial lung disease should be considered even in the face of a normal chest x-ray. The EKG invariably shows right ventricular hypertrophy. Chest x-ray may show enlarged central pulmonary vascular shadows. Echo will demonstrate an enlarged right ventricle in 2/3, and abnormal septal motion in 50%. Diagnosis is made by right heart catheterization, which, incidentally, is frequently complicated by malignant dysrhythmias. Patients who present with syncope or dizziness will have higher total pulmonary resistance (TPR); these patients have a poor prognosis. Perfusion lung scans should be performed to rule out unresolved large vessel pulmonary emboli; the most common perfusion scan pattern in PPH patients is a "mild patchiness" with no segmental defects.

The need for open lung biopsy is controversial. (Transbronchoscopic lung biopsy is contraindicated, because of the risk of hemoptysis.) Although open lung biopsy may rule out other occult diseases that may mimic PPH, such as recurrent thromboembolism, diffuse interstitial lung disease, and veno-occlusive disease, most of these will be detected by the basic work-up of physical exam, chest x-ray, PFT's, and perfusion lung scan. Whether the information from biopsy warrants the anesthetic risk (often high in PPH patients) must be decided on an individual basis.

A great area of controversy surrounds the question of whether medical therapy affects the course of the disease. Many authors advocate the use of anticoagulants (37) because of the predisposition to thrombus formation (right ventricular failure, inactivity) and the frequent finding of thromboemboli in lung biopsy material. Obviously, a small pulmonary embolus that might have little effect on a normal patient could have disastrous consequences for a patient with pulmonary hypertension. Improved survival with anticoagulation was noted in one study (38).

Adverse responses to vasodilators are common with "paradoxical" worsening of pulmonary hypertension; no clinical trial has demonstrated a survival benefit from vasodilator drug treatment (39). However, some studies report a consistent drop in pulmonary vascular resistance with therapy (without a drop in pulmonary artery pressure), and marked improvement in symptoms. Clearly, the time to examine the hemodynamic response to therapy in an individual patient is with in-hospital central monitoring with a pulmonary artery catheter. A 20% reduction of pulmonary vascular resistance with reduced or unchanged pressure should be documented before a particular vasodilator should be employed (36). Nifedipine, in particular, has proven to be the most effective drug; patients with Raynaud's phenomenon appear to respond particularly well (40). For end-stage illness in otherwise healthy patients, heart-lung transplantation should be considered.

PULMONARY HEMORRHAGE

Diffuse alveolar hemorrhage is a feature of several immune and idiopathic disorders: (42)

A. Antibasement membrane antibody (ABMA) disease

B. Vasculitides and collagen vascular disease

   1. Nonspecific systemic necrotizing vasculitis
   2. Systemic lupus erythematosus (SLE)
   3. Wegener's granulomatosis
   4. Henoch-Schönlein syndrome
   5. Polyarteritis nodosa
   6. Behçet's disease
   7. Essential mixed cryoglobulinemia
   8. Endocarditis - related vasculitis
   9. Tumor-related vasculitis
   10. Rheumatoid arthritis
   11. Progressive systemic sclerosis
   12. Mixed connective tissue disease

C. Idiopathic rapidly progressive glomerulonephritis (RPGN)

   1. Immune complex-mediated
   2. Without immune deposits

D. Chemical or drug-related

   1. D-penicillamine
   2. Trimellitic anhydride

E. Idiopathic pulmonary hemosiderosis

F. Miscellaneous

   1. Mitral stenosis

2. **Diffuse necrotizing infection (e.g. Aspergillus, Pseudomonas)**
3. **Severe coagulopathy**
4. **Acute leukemia**
5. **Fat embolism**
6. **Lymphangiography**
7. **Pulmonary embolus**
8. **Hemorrhagic pulmonary edema with renal failure**

The unifying pathophysiologic process is diffuse bleeding into the acinar portion of the lung. Patients present with hemoptysis, anemia, alveolar infiltrates on chest x-ray, dyspnea, and hypoxemia. This presentation is often initially confused with pneumonia or pulmonary edema, the syndrome being recognized only after the development of frank respiratory failure or major extrapulmonary involvement (e.g. glomerulonephritis). In differentiating pulmonary hemorrhage from other causes of hemoptysis and pulmonary infiltrates, therefore, one must 1) examine the clinical setting and 2) determine whether the alveolar filling process represents frank hemorrhage.

Active pulmonary hemorrhage often causes the hemoglobin level to fall by 2-4 g/dl per 24-48 hour period (43). Conversely, a stable hemoglobin in the face of progressive alveolar infiltrates practically excludes alveolar hemorrhage.

Patients with alveolar hemorrhage often have an elevated DLCO, because the large pool of extravascular erythrocytes will bind inhaled carbon monoxide. The test is limited, however, in that most patients do not have a baseline DLCO for comparison, and many are too ill to be tested properly.

Bronchoalveolar lavage (BAL) can reveal the characteristically abundant hemosiderin in the alveolar macrophages, although it takes 24-48 hours post-hemorrhage for the macrophages to engulf significant hemosiderin.

Differentiation of immune alveolar hemorrhage (IAH) and hemorrhagic pulmonary edema with renal failure and volume overload can be difficult. Evidence of major hemorrhage (large hemoptysis, abrupt fall in hemoglobin level, increased DLCO, grossly bloody BAL with abundant hemosiderin in macrophages) suggests IAH, and may constitute an indication for empiric therapy.

Although many diseases cause pulmonary hemorrhage, six account for the great majority of cases: (1) ABMA disease, (2) nonspecific systemic necrotizing vasculitis, (3) Wegener's granulomatosis, (4) SLE, (5) idiopathic RPGN, and (6) idiopathic pulmonary hemosiderosis.

Sixty to eighty percent of patients with ABMA have immune alveolar hemorrhage (IAH). Although renal function may be normal at the time of presentation, glomerular deposits of ABMA are always present, and microscopic hematuria is seen in 90%. Most patients develop frank nephritis. Diagnosis is most easily made by renal biopsy and serum assay of ABMA. Renal biopsy shows a nonspecific proliferative glomerulonephritis; the diagnosis is established by demonstrating linear deposits of IgG in glomeruli on immunofluorescence (IF) (46-50).

The alveoli will be filled with blood and hemosiderin - laden macrophages. Although no vasculitis is present linear deposits of ABMA can also be demonstrated along alveolar septa by IF. Lung biopsy is rarely needed, however, because of the high diagnostic yield from renal biopsy and serum assay of ABMA. Transbronchoscopic biopsy has been shown to be insensitive for demonstrating ABMA in the lung.

Treatment of ABMA disease has come full circle. It has long been recognized that corticosteroids and immunosuppressive drugs alone may stop pulmonary hemorrhage, but do not prevent end-stage renal failure. The addition of plasmapheresis to immunosuppressive regimens was then shown to arrest the deterioration of renal function, with renal outcome depending on the degree of impairment at the time therapy was initiated; non-oliguric patients with creatinines <7 do best. However, the data from recent randomized trials suggest that the addition of plasmapheresis to prednisone and cyclophosphamide is of only modest benefit. Leatherman suggests that combined plasmapheresis and immunosuppression be reserved for patients with ABMA who do not have advanced renal insufficiency at presentation. Pulse steroid therapy alone may be sufficient as initial treatment for patients who are not expected to recover renal function (oliguric, creatinine >7). Renal transplantation is a viable option for these patients once the serum ABMA level drops to zero.

Systemic necrotizing vasculitis (44) causes immune alveolar hemorrhage in association with glomerulonephritis, with skin, joint, GI, and CNS involvement. The renal vasculitis causes a focal and segmental necrotizing glomerulonephritis without immune deposits. The value of open lung biopsy is questionable because the vasculitis usually affects only the pulmonary capillaries, making pathologic recognition difficult. Therapy with steroids will lessen hemoptysis and stabilize the hemoglobin level within 24-48 hours. Cyclophosphamide should be added if there is significant renal or CNS involvement. Unlike ABMA disease, the renal failure is often reversible.

Wegener's granulomatosis (see below) has a presentation similar to systemic vasculitis, and even causes a similar renal lesion. Although granulomatous lesions of the upper and lower respiratory tract are characteristic, they may be absent in patients who present with IAH, in whom open lung biopsy may only show a pulmonary capillaritis. Therefore, since therapy with cyclophosphamide and prednisone is so effective in this disease (45), any patient who presents with IAH and a necrotizing renal vasculitis should be treated as if he had Wegener's granulomatosis, even without an open lung biopsy.

When immune alveolar hemorrhage occurs in SLE, the underlying diagnosis usually has been previously established. The only confusion in this setting is in differentiating IAH from nonimmune pulmonary disorders such as pulmonary hemorrhage from associated thrombocytopenia, pneumonitis with a drop in hemoglobin from intravascular hemolysis, and opportunistic pulmonary infections with blood vessel invasion (Aspergillus, Pseudomonas). A specific diagnosis is obviously essential, and may require open lung biopsy.

Idiopathic RPGN with pulmonary hemorrhage can mimic Goodpasture's syndrome (ABMA disease), but the renal biopsy will show a non-linear granular pattern (immune complexes) or, more often, no immune deposits. Pulsed steroid therapy is sufficient unless a necrotizing renal vasculitis is also seen, in which case the addition of cyclophosphamide should be considered.

Idiopathic pulmonary hemosiderosis is the only major cause of IAH that does not involve the kidneys. Open lung biopsy is useful in that vasculitis, granulomas, and immune complexes are absent. Recurrent hemorrhage can lead to interstitial fibrosis, though most patients survive for decades after diagnosis. Secondary causes, such as mitral stenosis, should be excluded by clinical means and echocardiography. Because spontaneous remissions are common, therapy is difficult to evaluate; although steroids in the acute setting seem to speed resolution of the alveolar hemorrhage, they do not affect the chronic phase of the disease. Chelation therapy, cyclophosphamide, and plasmapheresis have not been shown to be of benefit, except in the anecdotal case.

VASCULITIC DISEASE (1,16,23-26)

1. Wegener's Granulomatosis - Wegener's granulomatosis is a necrotizing vasculitis of the upper respiratory tract, lungs, and glomeruli (although involvement of all major organ systems has been described). Patients are usually male, and present with cough, fever, and an abnormal chest x-ray. Sinusitis and epistaxis are common. Renal disease is often asymptomatic, found only during evaluation. Severe hemoptysis is rare. The chest roentgenogram typically shows bilateral cavities and nodules.

Less common radiographic manifestations include diffuse interstitial lung disease, unilateral cavities, lobar collapse, pleural effusions or hilar masses. Ninety percent of patients eventually develop upper airway disease (sinusitis, rhinorrhea, "saddle-nose" deformities, granuloma formation). Renal disease is manifested by hypertension, azotemia, abnormal sediment, and proteinuria. Diagnosis is made by finding the characteristic granulomatous vasculitis in lung tissue. If lesions are present in the skin, upper respiratory tract, kidneys, or other organs lung biopsy may be avoided by biopsying a more accessible site of involvement. However, biopsy of extrapulmonary areas of involvement may only reveal a non-specific "leukocytoclastic vasculitis". In such an occurrence, the diagnosis must be confirmed by lung biopsy. Wegener's granulomatosis responds poorly to steroids alone. Cyclophosphamide usually induces a dramatic response within two weeks of therapy. Treatment is continued at least one year after induction of clinical remission.

2. Limited Wegener's Granulomatosis - Limited Wegener's granulomatosis is "Wegener's granulomatosis without the renal disease". However, this disorder may be a fundamentally different disease, as opposed to a "forme fruste" or mild expression of Wegener's granulomatosis. It usually responds well to steroids alone. Some patients stabilize without therapy.

3. Lymphomatoid Granulomatosis - Lymphomatoid granulomatosis clinically resembles Wegener's granulomatosis. However, on histology pleomorphic masses of invasive histiocytes and lymphocytes (rather than distinct granulomas) are found. Necrosis is unusual. Upper airway disease, if present, is usually much worse than in Wegener's granulomatosis, with perforations, ulcerations, and recurrent sinus infections being common. Septal and palatal involvement are often present. These features are quite uncommon in Wegener's granulomatosis. Renal involvement is not seen. Response to steroids and immunosuppressive agents is unpredictable. There is some risk for subsequent development of lymphocytic malignancies. Unlike Wegener's granulomatosis, any site of involvement should render the diagnosis on biopsy.

4. Benign Lymphocytic Angiitis and Granulomatosis - Benign lymphocytic angiitis and granulomatosis is "attenuated lymphomatoid granulomatosis". It is differentiated from lymphomatoid granulomatosis by virtue of its benign course, uncommon extra-pulmonary involvement, benign histology, and favorable response to chlorambucil. Diagnosis is made by biopsy, usually of lung tissue. Some authors consider benign lymphocytic angiitis and granulomatosis, lymphomatoid granulomatosis, and malignant lymphoma to represent a continuum of disease from benign to malignant.

5. Allergic Granulomatosis of Churg and Strauss - This disorder has often been characterized as "polyarteritis nodosa

with pulmonary involvement". A relationship between this disease and polyarteritis nodosa is not universally accepted, but there are many similarities between the two diseases. Patients with allergic granulomatosis of Churg and Strauss always have significant histories of asthma and eosinophilia. Their systemic vasculitis is identical to polyarteritis nodosa. Diagnosis is made by coupling the pulmonary history and clinical findings with biopsy of involved tissue. The biopsy should be obtained from extra-pulmonary sites if at all possible since lung biopsy may only show eosinophilic changes similar to Loffler's syndrome. Steroids are the mainstay of therapy. Cyclophosphamide is reserved for steroid failures. Response is similar to that seen in patients with "pure" polyarteritis nodosa.

6. Other Disorders - The complex syndromes described above are often difficult to separate one from another, but they have one common feature: inflammation of vessel walls. Some pulmonary diseases may manifest vascular involvement, but only as part of a more universal process involving other elements of the pulmonary parenchyma.

a. Bronchocentric Granulomatosis is a necrotizing granulomatous reaction of the bronchial wall that may secondarily invade adjacent vessels. It is seen in atopic patients with bronchopulmonary aspergillosis, but usually is clinically of little consequence other than leading to a biopsy of the lesion (since it appears radiographically as a mass). Steroids may be of benefit in symptomatic patients.

b. Necrotizing Sarcoid Granulomatosis, although considered by some to be a distinct entity, may actually be a vascular manifestation of sarcoidosis. Patients are usually asymptomatic and present with bilateral confluent pulmonary nodules. Hilar adenopathy is not usually discernible on radiographs, but nodal involvement with disease may be found on histologic examination. Steroids may be effective in the few cases requiring therapy.

c. Midline Granuloma (Lethal Midline Granuloma) deserves mention since it is commonly confused with Wegener's granulomatosis. It is a destructive granulomatous vasculitis involving only the upper airway; the lungs are not involved in the process. However, the evolution of midline granuloma to Wegener's granulomatosis or lymphomatoid granulomatosis has been described. The disease historically has been uniformly fatal unless treated. Good results are achieved with localized radiotherapy.

PULMONARY VASCULAR MANIFESTATIONS OF COLLAGEN-VASCULAR DISEASES (1,7,27-30)

The lung is secondarily involved in many systemic diseases including several of the collagen vascular disorders. The incidence and severity of pulmonary involvement varies from disease to disease within the family of collagen vascular disorders. In some, lung involvement is manifested only by microscopic changes in lung tissue. In others, overt derangements in pulmonary function are commonly seen. Hence, the presence of pulmonary disease in a patient with a collagen vascular disorder does not necessarily imply that the pulmonary derangement seen reflects lung involvement by the systemic process. Many of the collagen vascular diseases predispose the patient to other unrelated pulmonary complications. The first step in evaluating pulmonary disorders in patients with collagen vascular diseases is to assess he probability that the particular disease can cause the pulmonary disorder being evaluated.

Pulmonary Manifestations of Rheumatoid Arthritis

Rheumatoid arthritis is associated with both parenchymal and pleural involvement. It is unusual for rheumatoid arthritis to present solely with lung involvement; most patients have additional clinical evidence of rheumatoid arthritis. The rheumatoid factor is positive in over 80% of patients with lung disease. There are five types of lung involvement associated with rheumatoid arthritis:

1. *Pleurisy/Effusion* - Pleural involvement is the most common pulmonary manifestation of rheumatoid arthritis. Fifty percent of patients with rheumatoid arthritis have evidence of pleuritis at autopsy, but clinical disease is seen much less frequently. One-third of rheumatoid pleural effusions are asymptomatic, found only during routine evaluation. Effusions may be unilateral or bilateral. The effusions may resolve spontaneously, or fluid may persist for months to years. The pleural fluid usually contains both polymorphonuclear cells and monocytes in large numbers. The fluid typically is exudative, with a very low glucose level (usually < 25mg/100ml). The effusion may resolve with steroid therapy (usually given for other disease manifestations). The effusion can be treated by repeated aspirations. Rapid re-accumulation leading to respiratory compromise warrants pleurodesis. Decortication of loculated effusions which have caused fibrotic entrapment of lung is occasionally required.

2. *Necrobiotic Nodules* - The typical rheumatoid nodule in the lung is a pleural based mass ranging in size from a few millimeters to several centimeters in diameter. Occasional nodules may reach 5-7 centimeters in size. Necrobiotic nodules are usually bilateral, and frequently are associated with other pulmonary manifestations of rheumatoid arthritis. The nodules usually cause no symptoms, unless they are large enough to significantly compress or displace lung tissue. Cavitary nodules are not uncommon, and may be associated with cough, hemoptysis, pleural effusion, or (rarely) bronchopleural fistula.

Development of nodules may precede the arthritic manifestations of rheumatoid arthritis. Many patients develop concurrent subcutaneous nodules. Nodules from lung and skin are identical histopathologically. Therapy is probably indicated only for large or cavitary lesions, and even then the response to steroids is variable. Unfortunately, the finding of nodules in a patient with rheumatoid arthritis commonly presents the physician with a diagnostic dilemma, since the lesions mimic those seen in several malignant and infective processes. Thus, most lesions ultimately are diagnosed by biopsy.

3. Caplan's Syndrome - Originally described in Welsh coal miners, Caplan's syndrome presents as nodular opacities in the periphery of the lung in association with rheumatoid arthritis. The lesions appear rapidly in "crops", often in association with arthritic manifestations and subcutaneous nodules. The disease has also been described in other pneumoconioses. The nodules are similar histologically to necrobiotic nodules, but often have "dust" in the necrotic areas of tissue. Most nodules are asymptomatic.

4. Diffuse Interstitial Lung Disease (Rheumatoid Lung) - Approximately 2% of patients with evidence of rheumatoid arthritis have chest roentgenograms showing diffuse interstitial lung disease. Forty percent of rheumatoid arthritis patients have abnormal pulmonary function tests. The likelihood of developing rheumatoid interstitial lung disease increases in proportion to the clinical severity of rheumatoid arthritis. The typical radiograph shows a generalized interstitial infiltrate, with the lower lung fields most affected. Many patients are asymptomatic. Symptomatic patients manifest the usual clinical picture of interstitial lung disease. Fever, pleurisy, and hemoptysis are uncommon; when present, they usually represent manifestations of one of the other lung disorders seen in rheumatoid arthritis. The interstitial disease may precede all other clinical manifestations of rheumatoid arthritis, occasionally by several months or years. Histologically a nonspecific "UIP" picture is seen on biopsy. Some patients progress to end-stage interstitial fibrosis; many remain stable or manifest slow deterioration in lung function. The response to steroids is variable.

5. Pulmonary Arteritis - Rarely, the principal pulmonary manifestation of rheumatoid arthritis will be one of pure vasculitis (arteritis). Patients present with a syndrome similar to primary pulmonary hypertension. Progression of disease is variable; response to steroids is not well documented.

Systemic Lupus Erythematosus

The lungs and pleura are involved more commonly in systemic lupus erythematosus (SLE) than in any other collagen vascular disease (50-70%). Several processes are seen:

1. Lupus Pleuritis/Effusion- At least 50-75% of patients with systemic lupus erythematosus will manifest pleuritic signs or symptoms sometime during the course of their disease. Pleural disease is usually painful (in contradistinction to rheumatoid arthritis), and is commonly associated with a flare of the underlying disease. Pleural effusions are typically small and bilateral. The fluid is exudative, and usually has no diagnostic characteristics. The effusions respond to steroids but infection must be ruled out prior to treatment.

2. Atelectasis - Basilar atelectasis is common in systemic lupus erythematosus patients, usually in association with evidence of pleuritis. Manifestations and therapy are similar to non-lupus causes of atelectasis.

3. Uremic Pulmonary Edema - Although not due to primary pulmonary involvement by systemic lupus erythematosus, uremic pulmonary edema warrants mention since severe renal involvement with SLE is common.

4. Acute Lupus Pneumonitis - A diagnosis of exclusion, acute lupus pneumonitis may be confused with atelectasis, pulmonary edema, or infection. The radiographic expression of the syndrome is one of poorly demarcated infiltrates (usually alveolar), with or without effusions. Tachypnea, fever, and hypoxemia are common. Symptoms may develop suddenly, and the patient may appear extremely ill. Most patients respond to steroids. Prior to therapy, however, a detailed evaluation is necessary to rule out infection as the etiology for the patient's syndrome. Many patients require open lung biopsy to exclude opportunistic infections. Invasive hemodynamic monitoring is frequently required, both to rule out occult pulmonary edema and to manage the critically ill patient.

5. Diaphragmatic Dysfunction - A diffuse myopathy involving the muscles of the diaphragm is occasionally seen in systemic lupus erythematosus. Patients present with orthopnea. Pulmonary function testing shows a restrictive process. Progression of this myopathic disorder has not been reported.

Progressive Systemic Sclerosis (Scleroderma)

Most patients with progressive systemic sclerosis will manifest clinical or radiographic evidence of pulmonary involvement; 100% will have interstitial fibrosis at autopsy. Patients present with the usual signs, symptoms and laboratory findings of interstitial lung disease. Many patients develop pulmonary hypertension. Pleural effusions are rare. Esophageal dysmotility may lead to pulmonary manifestations caused by recurrent aspiration.

Polymyositis/Dermatomyositis

Fewer than 5% of patients with polymyositis/dermatomyositis have pulmonary involvement. The pulmonary manifestation of polymyositis/dermatomyositis is that of diffuse interstitial lung disease. Effusions have not been described. Unlike progressive systemic sclerosis (or many other syndromes associated with interstitial lung disease), the pulmonary manifestations of polymyositis/dermatomyositis frequently respond to steroids. Response is usually greater if the disease is treated during its inflammatory (as opposed to fibrotic) stage. Recurrent aspiration (due to muscle weakness) is common in polymyositis/dermatomyositis.

Sjögren's Syndrome

Many patients with Sjögren's syndrome will manifest pulmonary symptoms or abnormalities. Since Sjögren's syndrome is typically seen in association with manifestations of other collagen vascular diseases (rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis/dermatomyositis), many of the pulmonary manifestations are those seen in the associated disorder. The most common manifestations are as follows:

1. Pleurisy/effusion - The pleuritic component of Sjögren's syndrome is found in 15% of patients. Manifestations are identical to those seen in rheumatoid arthritis or systemic lupus erythematosus.

2. Interstitial Fibrosis - Interstitial disease seen in Sjögren's syndrome is similar to that seen in rheumatoid arthritis.

3. Dessication - Lymphocytic infiltration of tissue is a hallmark of Sjögren's syndrome. The most common site is the salivary glands. The mucous glands of the tracheobronchial tree may also be invaded, leading to atrophy with resultant inspissated secretions. Atelectasis and secondary infections may result. Patients may develop chronic cough and recurrent bronchitis. Symptomatic patients typically manifest small airways obstruction on pulmonary function testing. Response to bronchodilators is variable. Some patients respond to steroids.

4. Lymphoid Interstitial Disease - Rarely, interstitial infiltration with lymphocytes occurs in Sjögren's syndrome. Patients present with signs and symptoms similar to those seen in diffuse interstitial lung disease caused by rheumatoid arthritis. However, lung histology shows a spectrum of lymphocytic infiltration ranging from lymphocytic interstitial pneumonitis to pseudolymphoma to lymphoma. The more "benign" pathologic entities are treated with steroids or immunosuppressive agents, usually with good response. A diagnosis of malignancy warrants aggressive chemotherapy.

Mixed Connective Tissue Disease

Mixed connective tissue disease is an "overlap" syndrome with concurrent features of progressive systemic sclerosis, systemic lupus erythematosus, and polymyositis/dermatomyositis. Typical manifestations of pulmonary involvement are pleural effusions and interstitial lung disease. Steroids are usually effective.

Ankylosing Spondylitis

Ankylosing spondylitis is a chronic progressive inflammatory disease of the large joints of the axial skeleton. There are two pulmonary manifestations seen in ankylosing spondylitis:

1. Thoracic Restriction - Chest wall restriction in ankylosing spondylitis is due to fusion of the costovertebral joints. Unlike kyphoscoliosis, the resulting pulmonary function abnormalities are usually not severe. Lung volumes are typically only slightly or moderately decreased.

2. Interstitial/Bullous Disease - Up to 30% of patients with ankylosing spondylitis manifest abnormalities of pulmonary parenchyma. Early changes include apical pleural thickening and apical interstitial infiltrates. The disease usually begins in one upper lobe but becomes bilateral as the disorder progresses. Subsequent cavity or cyst formation is common. Progression of the disease is variable. Severe disease associated with hilar retraction, fibrosis, and bi-apical pleural thickening may mimic tuberculosis roentgenographically. The lung histology is one of chronic inflammation and fibrosis. Most patients remain asymptomatic. There is no therapy. Many patients, however, may acquire secondary infections with *Aspergillus* or atypical mycobacteria. Surgical resection for massive hemoptysis may be required. Resection frequently is complicated by chronic empyema or bronchopleural fistula.

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PULMONARY EMBOLISM

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INTRODUCTION

Pulmonary embolism (PE) is a frequently considered diagnosis for a patient who presents with a variety of complaints including shortness of breath, chest pain, mental status changes, EKG changes and hemoptysis. Although accurate statistics are not available, commonly quoted figures suggest an incidence of approximately 630,000 cases yearly in the United States (1,2). Of these cases, as represented in Figure 1, 11% die within the first hour. Of the remaining 89%, a diagnosis is made in only 29% of these cases. When a diagnosis of pulmonary embolism is confirmed and therapy instituted, 92% of treated patients survive. On the other hand, if the diagnosis of pulmonary embolism is missed and the condition goes untreated, it has an associated mortality of 30%.

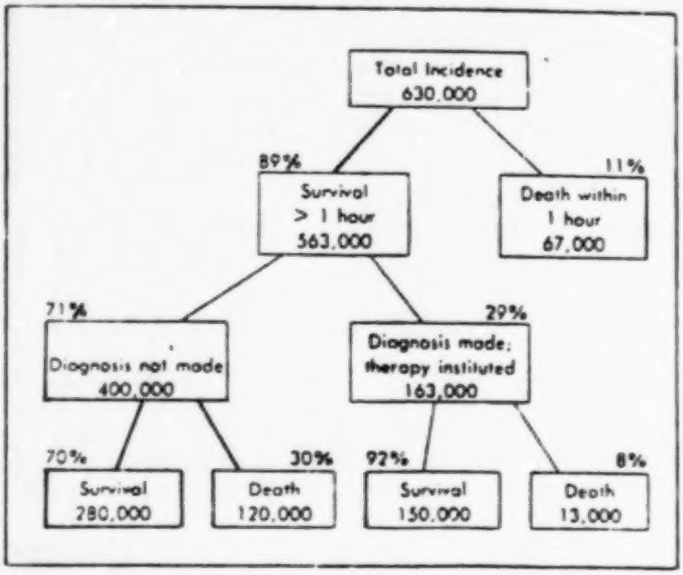

Total Incidence
630,000
89%
Survival
> 1 hour
563,000
11%
Death within
1 hour
67,000
71%
Diagnosis not made
400,000
29%
Diagnosis made;
therapy instituted
163,000
70%
Survival
280,000
30%
Death
120,000
92%
Survival
150,000
8%
Death
13,000

Fig 1. Incidence of pulmonary embolism per year in the United States.

PREDISPOSING FACTORS

In the past it was not generally recognized that virtually all PE (greater than 90%) originate in the popliteal or iliofemoral veins. In addition, it was not recognized that large emboli could reside in these locations in the face of a negative leg exam. Unfortunately, greater than 50% of lower extremity deep venous thrombi (DVT) are undetectable by clinical exam (4). The only signs that confidently point to thrombi are inflammation or high-grade obstruction, signs which are often absent. However, with the advent of 125-I-fibrinogen scanning, impedance plethysmography and venous Doppler studies, a greater knowledge of those at risk for PE and the manner of evolution of DVT has been acquired. Factors predisposing to DVT include congestive heart failure, acute myocardial infarction, bacteremic or non-bacteremic shock, obesity, estrogens, malignancy, polycythemia vera, dysproteinemia, surgery, anesthesia, immobilization (includes prolonged standing or sitting), pregnancy, diabetes mellitus, burns, trauma (especially fractures of the spine, pelvis, or legs), varicose veins and previous PE. More uncommon predisposing entities include sickle cell anemia, homocystinuria (virtually all have thromboembolism at death), and paraneoplastic syndromes. Antithrombin III deficiency may be a relatively common predisposing factor for venous thrombosis accounting for 2% of all clinical episodes of thromboembolic disease (59). In AT III deficiency, pulmonary emboli can theoretically form in situ in the pulmonary arteries themselves. This could lead to the unusual clinical situation in which IVC interruption may fail to prevent further embolic episodes. Other rare causes of hypercoagulable states include protein C and protein S deficiencies, increased levels of Factor V and Factor VII (49,50), increased platelet adhesiveness with decreased platelet survival (51), and the presence of abnormal plasminogens, excessive levels of plasmin or plasminogen inhibitors (52-54). Recognition of predisposing factors is important in the evaluation of a patient for possible PE. In the Urokinase Pulmonary Embolism Trial (UPET), 94% of patients with documented emboli had one or more predisposing factors.

With the advent of 125-I-fibrinogen scanning, it has become apparent that DVT typically originate in calf veins. The following clinical settings and the percentage occurrence of venous calf thrombi associated with each reveal how frequently thrombi develop: major abdominal surgery (1-33%), thoracic surgery (26-65%), gynecologic surgery (14-19%), hip surgery (48-74%), acute myocardial infarction (30-40%), post CVA with paralyzed lower extremity (60%), postpartum (3%), and postop patient with previous postoperative embolism (70-90%) (8). Venous calf thrombi may form intra-operatively or within the first 24 to 48 hours postoperatively.

Fortunately most of these calf thrombi resolve within the calf. Thrombi that embolize do not dislodge directly from calf veins; rather, they embolize from clot propagating into the thigh or higher. Five to twenty percent of calf vein thrombi propagate into thigh veins, and of these thrombi, 50% embolize. Consequently, only about 3-10% of calf vein thrombi will ultimately result in pulmonary emboli (5). Although venous calf thrombi form within the first 24 to 48 hours after surgery, PE usually do not occur until 4-20 days later.

Despite frequent recognition of thrombi in axillary and subclavian veins, less than one percent of pulmonary emboli originate from these sites (2). Likewise, lower extremity superficial thrombophlebitis does not result directly in pulmonary embolization. However, 20% of those with superficial thrombophlebitis have associated deep vein thrombi (5). The origins of pulmonary emboli have only been discovered as a consequence of the advent of non-invasive tests which are capable of detecting early DVT. The details of these techniques which include Doppler studies, impedance plethysmography, and 125-I-fibrinogen scans are beyond the scope of this article. Only within the last 12-13 years have non-invasive means of evaluating the impact of prophylactic therapy been developed. Because prophylaxis of DVT means prophylaxis of PE, these techniques are of considerable import. For the interested reader, further references regarding these techniques are included (4, 9-13).

PATHOPHYSIOLOGY

The significant pathologic consequences of PE are hemodynamic and respiratory. The hemodynamic consequences depend strongly on the pre-embolic state of the individual, i.e., cardiac status and integrity of the pulmonary vascular bed. In normals 60% of the pulmonary vasculature may be obstructed before right ventricular overload occurs. In the patient with chronic obstructive lung disease and tenuously controlled cor pulmonale, however, a small embolus may be fatal. Forty percent occlusion (the equivalent of obstructing two lobar arteries) is arbitrarily considered to be massive. The mean pulmonary arterial pressure is found to be greater than 20 torr in 70% of patients who have PE. In normals , mean pulmonary arterial pressure never exceeds 40 torr even with massive occlusion, because a normal right ventricle simply cannot generate greater pressures. In patients with pre-existing cardiopulmonary disease mean pulmonary arterial pressures greater than 40 torr are common. Pulmonary hypertension is not likely to ensue with less than 20-30% obstruction. In summary, the hemodynamic consequences of PE result from reduction in available cross-sectional area, associated hypoxemia, and the effects of mediator release from impacted platelets. These changes lead to increases in pulmonary vascular resistance, pulmonary arterial pressure, and right ventricular work.

The respiratory consequences of PE include increased alveolar dead space, and therefore an increased V/Q ratio. Stimulation of lung irritant receptors by platelet mediators may also produce reflex bronchoconstriction. The lower lung volumes produced by generalized pneumoconstriction result in slight reductions of central airway diameter and therefore slight increases in airway resistance. If a pulmonary artery remains occluded, surfactant production ceases immediately, but any local deficiency takes approximately 24 hours to develop. Surfactant loss results not only in atelectasis but also increased capillary permeability, allowing extravasation of fluid and red cells into the embolized area. If embolic obstruction is not total, surfactant loss is minimized. This mechanism may explain why some patients develop "congestive atelectasis" i.e., infiltrate(s) on chest x-ray, (typically about 24 hours post-embolus) and others do not (17).

DIAGNOSIS

The diagnosis of pulmonary embolism based on history and physical exam is extremely unreliable, as many cardiopulmonary disorders mimic pulmonary embolism. Clinical clues are too nonspecific for the definitive diagnosis of PE. Bell et al (14), reviewed the signs and symptoms found in 327 patients with angiographically documented PE and reported the following findings:

Symptoms	Percent of Patients
Chest pain	88%
- Pleuritic	74%
- Nonpleuritic	14%
Dyspnea	84%
Apprehension	59%
Cough	53%
Hemoptysis	30%
Diaphoresis	27%
Syncope	13%
Signs	
Respirations >16/minute	92%
Rales	58%
Increased P2	53%
Tachycardia	44%
Temp >37.8OC	43%
Phlebitis	32%
Cyanosis	19%

These signs and symptoms are common findings in many patients, and those sensitive for PE are very nonspecific.

One perplexing sign in a patient who presents with an apparent PE is fever. Murray et al reviewed the occurrence of fever associated with pulmonary embolism in 1979 (60). Upon review of 35 patients with angiographically documented PE, fever, defined as a rectal temperature >38o C, was present in 64% of their patient population. The febrile course of the patients in their study is best outlined in figure 2.

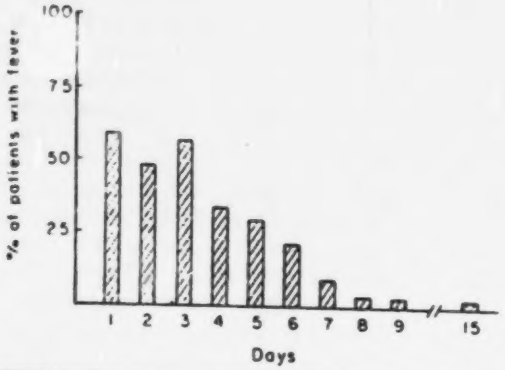


Figure 2. Per cent of 31 patients (groups I and II) with fever (rectal temperature ≥38°C) by hospital day.

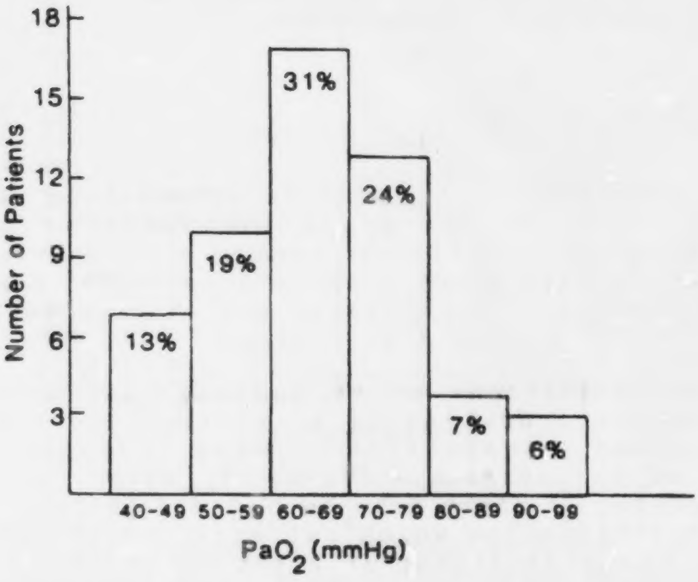
AJM 67:233, 1979.

These authors concluded: 1) fever in association with PE is common, 2) there is an increased incidence of pulmonary infarction syndrome in patients who present with a fever (75% of their patients), 3) high grade temperatures (>39o C) were found in 25% of their patient population, and 4) high temperatures seldom (<10%) persist greater than 7 days.

Cardiac manifestations of PE include: supraventricular arrhythmias (atrial fibrillation or flutter) in 15%(15); EKG changes including nonspecific T-wave changes in 42%; manifestations of cor pulmonale (S1-Q3-T3, right bundle branch block, P pulmonale, or right axis deviation) in less than 20%; and a cardiac examination which reflects right ventricular overload (67). Manifestations of right ventricular overload include fixed splitting of second heart sound with accentuated P2, tricuspid regurgitation and evidence of central venous hypertension with dependent edema, ascites and hepatic congestion.

The chest radiograph in PE is usually unchanged from baseline. However, a variety of radiographic signs may be present and may add telling clues. The most common radiographic abnormality (45%) associated with PE is elevation of one or both hemidiaphragms. The mechanism underlying elevation of a hemidiaphragm remains unknown. Some authors attribute it to pneumoconstriction with volume loss, while others attribute it to splinting from pain (7,17). Other "classic" but uncommon findings include focal oligemia (Westermark's sign), plate-like atelectasis, Hampton's hump (a pleural-based triangular infiltrate with the apex pointed at the hilum, due to infarction), pleural effusion(s), and central pulmonary arterial enlargement greater than 16mm (due to dilatation of the vessel by bulk thrombus - not due to increased pulmonary artery pressure). An abrupt cut-off of a pulmonary artery may be seen as the so-called "knuckle sign" (7).

In a patient with suspected PE, an arterial blood gas should be routinely obtained. However, the UPET study demonstrated that approximately 11-13% of the patients with significant PE had arterial oxygen tensions above 80mmHg. Thus, as demonstrated in Figure 3, a normal arterial oxygen tension does not rule out PE, especially if the patient has no prior history of cardiopulmonary disease.



Chest 81:495-501, 1982

Figure 3: Arterial pO2 from 54 patients with no prior history of cardiovascular disease and angiographically documented PE.

In a patient with underlying cardiopulmonary disease an arterial pO2 >80mmHg indicates a very low probability of PE. The AaDO2 should be calculated in all patients with suspected PE and if widened may lend credence to the diagnosis (68). In summary, arterial hypoxemia is commonly found in patients who have experienced a PE, however it is not an inevitable consequence of embolism and its extent depends on the severity of vascular obstruction.

At this point we have discussed the incidence of PE, clinical signs and symptoms associated with PE, and how routine laboratory and radiographic studies may be altered by a PE. As mentioned, none of the latter findings is specific for the diagnosis of PE. In effect, it can be concluded that the clinical evaluation serves only to suggest the possibility of embolism and to direct further studies to support or refute the diagnosis.

Several radiographic imaging modalities are available which are employed to confirm or rule out pulmonary embolism. The two most frequently used are ventilation-perfusion (V-P) scintigraphy and pulmonary angiography.

VENTILATION - PERFUSION SCANNING (V-P)

Perfusion lung scanning, a very sensitive but nonspecific method of detecting abnormalities of pulmonary perfusion, became clinically available in the 1960's. Technically the procedure is easy to perform, technetium-99m labelled macroaggregated albumin being injected intravenously into a supine patient. The distribution of the particles trapped in the pulmonary capillary bed reflects the distribution of pulmonary blood flow. Multiple studies have confirmed the axiom that a normal perfusion scan rules out a clinically significant PE (2,6,17,22). Kipper et al reconfirmed this belief by following 68 patients with a negative perfusion scan for a mean of 30.2 months after a clinically suspected PE (66). Only one of the 68 patients received anticoagulation (for deep venous thrombosis). At the end of the study period, none of the patients had experienced an apparent thromboembolic event, supporting the belief that a normal perfusion scan essentially rules out pulmonary embolism, and that further evaluation for possible PE is not warranted.

Ventilation imaging is ostensibly used to improve the specificity of perfusion scintigraphy in patients with suspected pulmonary embolus. Xe-133 is the most widely used ventilation imaging agent. Ventilation studies with Xe-133 are usually performed prior to perfusion studies and require a relatively stable, cooperative patient as breath holding is necessary. There are no uniformly accepted criteria for the diagnosis of PE by V-P scanning. However, the scheme proposed by Biello et al (62) has gained the most widespread acceptance. In Biello's study, the results of V-P imaging and pulmonary angiography were compared in 146 patients with clinically suspected PE and a scheme for the interpretation of V-P studies was postulated. The study group represented a selected subset of patients in whom: 1) the diagnosis of PE remained in doubt after V-P scanning, or 2) patients in which anticoagulation was contraindicated and possible surgical intervention was being considered. Both groups required pulmonary angiography on the basis of an abnormal V-P scan. Of one hundred and forty-six patients who were in the study group, all with abnormal V-P scans, 53 (36%) had angiographically documented PE. V-P scans were subsequently classified as low probability (<10%) for PE, indeterminate probability, and high probability (>85%) for PE by comparison of angiographic studies and V-P scan patterns. The proposed scheme developed by Biello et al is seen in Figure 4.

TABLE 4: Scheme for Interpretation of V-Q Imaging

Interpretation	Pattern	Frequency of Pulmonary Embolism (%)
Normal	Normal perfusion	0*
Probability of pulmonary embolism:		
Low	Small V-Q mismatches	0
	Focal V̇-Q̇ matches with no corresponding radiographic abnormalities	4.8
	Perfusion defects substantially smaller than radiographic abnormalities	7.7
Intermediate	Diffuse, severe airway obstruction	20
	Matched perfusion defects and radiographic abnormalities	27
	Single moderate V-Q mismatch without corresponding radiographic abnormality	33
High	Perfusion defects substantially larger than radiographic abnormalities	87
	1 or more large, or 2 or more moderate-sized V-Q mismatches with no corresponding radiographic abnormalities	92

Figure 4: Scheme for interpretation of V-P imaging
AJR:133, 1036, 1979

Biello classified defects as "large" (segmental) if greater than 75% of a segment was involved, "moderate" (subsegmental) if 25-75% of a segment was involved, and "small" if less than 25% of a segment was involved. Pulmonary embolic perfusion defects normally have several other "classic" characteristics: 1) wedge shaped and pleural based defects, 2) conformation to bronchopulmonary segmental anatomy, 3) multiple defects (80% have two or more perfusion defects) and 4) V-P mismatching (69). The application of V-P scan probabilities to a particular clinical situation must include pretest probability of PE and risk benefit analysis of treatment versus nontreatment. An indeterminate V-P scan, in most cases, commits the clinician to further diagnostic studies to include a pulmonary angiogram. Many would consider that a low probability scan is not of sufficient predictive value in a disease of this severity, and needs further confirmation as well.

PULMONARY ANGIOGRAM

In 15-35% of patients subjected to V-P scanning a definitive diagnosis of PE is not established and, in most cases, further evaluation in the form of pulmonary angiography is indicated. Pulmonary angiography is considered to be the "gold standard" in diagnosing PE (20,25). Typical situations in which a pulmonary angiogram is necessary include the following:

1. For surgical vena cava ligation or pulmonary embolectomy.

2. If the patient is a very high-risk candidate for heparin (GI-bleed, post-surgical, etc.).

3. Low probability or indeterminate V-P scan in the face of high clinical suspicion for PE.

4. In any person 25 years or younger. (Not universally accepted criterion).

5. V-P scan showing a single segmental or lobar defect. (Most PE are bilateral and multiple. Seventy-eight percent of PE in Urokinase trial were bilateral (18). A single defect is thus a soft criterion for PE).

Angiography is an invasive procedure and is not diagnostically foolproof; unlike perfusion scanning it is more specific than sensitive, so that a normal angiogram doesn't entirely rule out thromboembolism. However, in skilled hands it only rarely produces false negative results (28). It is subject to interpretation limitations, but one study showed less than 6% interobserver disagreement (22). Using superselective injections (segmental angiography) and magnification filming, angiographic defects as small as 0.5mm may be detected. Defects smaller than this are thought to be clinically insignificant. There are significant practical limitations including availability, the specific technique(s) by which it is performed, and the experience of the interpreter. Availability is of key importance as undue delay may allow embolic resolution and an erroneously negative result. Most emboli, however, remain subject to visualization for 72 hours. The only diagnostic findings are abrupt cut-off of a vessel or a filling defect. An additional advantage of pulmonary arteriography is the ability to measure right heart pressures and calculate pulmonary vascular resistance. Morbidity and mortality of pulmonary arteriography are approximately 3% and 0.3%, respectively (29). The procedure carries much less risk than subsequent anticoagulation. Therefore, angiography should be considered a relatively low risk method for defining the need for the greater risk of anticoagulant therapy. Two large studies have revealed that when PE is absent on pulmonary angiogram, anticoagulation is unnecessary. These patients uniformly do well with less than a 2% chance of subsequent embolization (25,28).

PULMONARY INFARCTION

Eighty-five percent of PE are multiple with a slight predisposition to affect the right lung. Because of pulmonary blood flow patterns, emboli also have a predisposition to enter the basilar segments. Pulmonary infarction is rare, occurring in only 10-15% of patients with pulmonary emboli, and can be definitely diagnosed only at autopsy. Infarction is uncommon because the area of embolized lung can be adequately oxygenated by 1) collateral pulmonary arterial supply; 2) bronchial arterial supply; and/or 3) oxygen via the airways. Because they may lodge distal to collateral anastomoses, small emboli are more likely to cause infarction. (Left ventricular failure does not appear to be associated with a higher incidence of infarction, contrary to earlier belief). Pulmonary infarction results in a bloody pleural effusion in only about 30% of the cases.

PHARMACOPHYSIOLOGY

An embolus is a thrombus covered with platelets and thrombin, the interior of which is composed of a fibrin meshwork, plasminogen, trapped red cells, and platelets. Embolus impaction results in platelet degranulation with release of serotonin, adenine nucleotides, histamine, catecholamines, thromboxanes, and prostaglandins (17,29). These substances may stimulate various neural lung structures including J-receptors and irritant receptors of the airway, thereby contributing to the dyspnea, tachypnea, and cough characteristically seen in pulmonary embolism. The extent to which these mediators result in reflex pneumoconstriction in the embolized areas remains a subject of controversy. Most authorities agree however that pneumoconstriction, if present, is most likely the result of these mediators (2,6,17). The extent to which pulmonary emboli hamper the nonrespiratory (metabolic) functions of the lung is unknown.

TREATMENT

The treatment of PE can be subdivided into four areas: 1) prevention, 2) anticoagulation, 3) thrombolytic therapy, and lastly 4) invasive or surgical therapy.

The best treatment for PE is prevention. As noted previously, the hospitalized patient is at increased risk of venous thromboembolism. Multiple studies have demonstrated that low dose heparin (5,000 units twice daily) is efficacious in reducing mortality from pulmonary embolism in post surgical patients (except hip surgery), post myocardial infarction patients, respiratory intensive care unit patients and in immobilized general medical patients (8, 31-35, 70). The proposed mechanism of action of low dose heparin is the activation of small amounts of antithrombin III which has significant anti-factor Xa activity resulting in reduced thrombogenesis.

When pulmonary embolus is suspected and no contraindications to anticoagulation are present, heparin therapy may be initiated prior to definitive diagnostic studies. Heparin is essentially a form of preventive therapy which retards further thrombus growth while the body's own fibrinolytic mechanisms reduce thrombus size and establish organization of thrombus within the vessel wall. Heparin is normally started with a loading dose of 10,000-15,000 units intravenously followed by a constant infusion of 1,000 to 2,000 units an hour. The goal of therapy is to maintain the activated partial thromboplastin time 1 1/2 to 2 1/2 times normal. Initially, for 48-72 hours, higher doses of heparin may be required to overcome the "intrinsic heparin resistance" often noted in the presence of a large thrombotic load. Constant infusion heparin is generally thought to be superior to intermittent intravenous therapy. In one controlled prospective trial major bleeding was seven times less frequent with constant infusion heparin than with intermittent boluses, while both were equally effective in preventing further emboli (45). However, the methods were not truly comparable, since the intermittent group received far higher daily doses of heparin. Other studies have shown a higher incidence of recurrent PE after continuous infusion of heparin than after intermittent heparin therapy. This area remains controversial (57). Heparin therapy is usually given for a full ten days but has been found to be equally effective if given for only five days when coumadin anticoagulation is established simultaneously. The patient is kept at bed rest for 4-5 days after which time progressive ambulation may be resumed.

Heparin is a heterogeneous mucopolysaccharide with a half-life of 90 minutes; activity is confined to the intravascular space. It is removed by the reticuloendothelial system. Heparin promotes anticoagulant activity by complexing with AT III which subsequently binds to thrombin, plasmin and factors IX, X, and XI, thus inhibiting thrombin induced fibrinogen polymerization and clot formation. In addition, heparin possesses antiplatelet activity and is a serotonin antagonist. Therefore, it may ameliorate some of the adverse effects caused by the release of serotonin and other humoral mediators from platelets adherent to the thrombus (71). Complications associated with heparinization include a 12.8% incidence of non-fatal bleeding noted in a 10-day course of therapy, 0.1% incidence of fatal bleeding, and a 5-30% incidence of thrombocytopenia (59). Factors associated with an increased risk for bleeding complications include female sex, aspirin use, significant alcohol use and underlying disease. Possible contraindications to heparinization are found in Figure 5.

Contraindications to Anticoagulation

Absolute
- Intracranial hemorrhage, malignancy or arteriovenous malformation
- Active internal bleeding

Relative
- Recent major surgery, trauma or deep biopsy*
- Pregnancy and the postpartum period
- Preexisting hemorrhagic tendency
- Uncontrolled severe hypertension
- Other potential bleeding risks (eg, a history of peptic ulcer disease)

*Within two weeks

Figure 5: Chest 86(1), 106, 1984.

Another form of treatment currently available for use in patients with PE is thrombolytic therapy utilizing either streptokinase or urokinase. In the late 1960's the Urokinase Pulmonary Embolism Trial (UPET) Phase I study was performed comparing a 12 hour infusion of urokinase followed by heparinization versus heparinization alone. In this study, 160 patients were randomized into the two treatment groups. The data clearly demonstrated that urokinase therapy was superior to heparin alone in achieving angiographic evidence of clot lysis, reversion towards normal of hemodynamic abnormalities and improved pulmonary perfusion as measured by lung scanning. Surprisingly, however, the mortality for both groups was not statistically different, while the urokinase group had a significantly higher incidence of bleeding complications (45% versus 17%) (72). A follow-up study, the Urokinase-Streptokinase

Embolism Trial (USET) compared 12 hour infusions of urokinase with 24 hour infusions of urokinase and 24 hour infusions of streptokinase. In this study a total of 167 patients were randomized into the three treatment groups. The study found that clot resolution with 24 hours of urokinase was no better than that with a 12 hour infusion. Neither urokinase nor streptokinase was significantly superior when overall results were compared; however, as in the Phase 1 study both were superior to heparin alone in causing early clot lysis (64).

At the present time, in the setting of pulmonary embolism, thrombolytic therapy is recommended primarily for the patient with a massive embolus which has resulted in systemic hypotension or which occludes 50% or more of the pulmonary arterial circulation, such that another embolus would be fatal. Guidelines with regards to streptokinase use and contraindications are outlined in an excellent article by Ball (42).

Surgical intervention in pulmonary embolism can be divided into two categories: 1) procedures aimed at preventing propagation of future thrombi to the lungs, and 2) procedures to remove clots already present in the pulmonary vascular bed. With regards to the latter, emergency pulmonary embolectomy is now seldom performed. Both thrombolytic therapy and heparin anticoagulation (47) have been shown to be superior forms of therapy when compared to emergency pulmonary embolectomy and result in lower mortality rates (mortality of pulmonary embolectomy is 65-70%) (6). Emergency pulmonary embolectomy may be considered, however, when anticoagulant therapy has failed or is contraindicated and 1) hypotension and hypoxemia persist despite vasopressors and oxygen, 2) there is evidence of decreased function of vital organs such as brain and kidney (urine output <20 ml/hr), and 3) there is angiographic proof of obstruction of > 50% of the pulmonary vascular bed with emboli that can be reached in the main right or left pulmonary artery (58).

Caval interruption has been based on two postulates: 1) the procedure would prevent embolic recurrence, and 2) recurrence of emboli would inevitably lead to severe compromise of the pulmonary vascular bed. Neither of these postulates has been borne out. Ligation of the vena cava leads to relatively prompt development of large collaterals including ovarian, spermatic, vertebral, and superficial abdominal veins.

Partially interruptive procedures utilizing clamps, umbrella devices, plications, and "memory metal" may be effective in preventing massive emboli from reaching the lungs but may lead to other complications as well. These devices continue to allow small emboli to gain access to the pulmonary vasculature. The incidence of recurrent PE in patients who have had vena cava procedures lies somewhere between 0-20% (48). These appliances may serve as sources of thrombi themselves, and do not obviate the need for anticoagulant therapy unless it is otherwise contraindicated. Finally, a substantial percentage of partial interruptive procedures (30% or more) are converted to total occlusion by thrombosis with the subsequent development of large collaterals (2); this is not a significant problem with the Kim-Ray-Greenfield filter, which most consider to be the method of choice if surgical interruption is indicated.

Faced with these considerations, caval interruption probably should be peformed only as a lifesaving maneuver when active bleeding contraindicates anticoagulant therapy; when septic emboli of non-cardiac origin are present; or when recurrent pulmonary embolism recurs despite adequate anticoagulation.

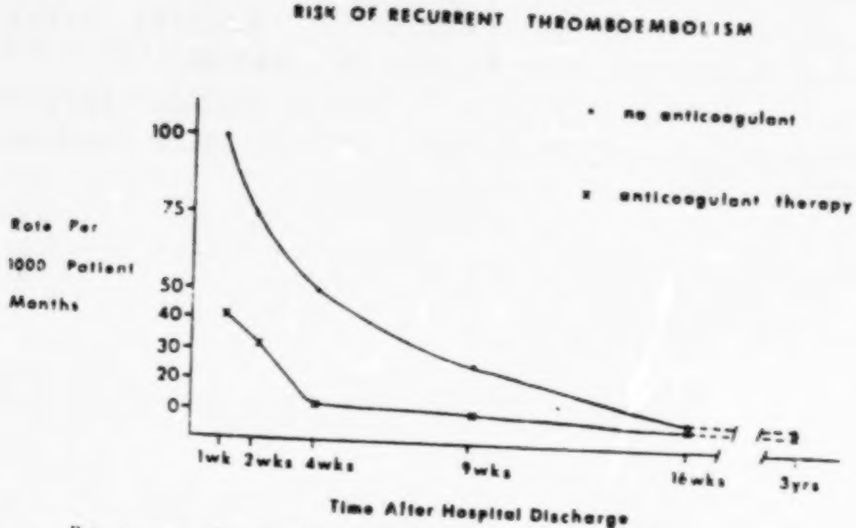
A recurrent PE when "adequately anticoagulated" is a very uncommon finding. In up to 40% of patients labeled as "anticoagulant failures", subsequent evaluation found the patients to be inadequately anticoagulated. In this group of patients, adjustments to ensure that they are adequately anticoagulated should be made before caval interruption is considered.

In general, when caval interruption is considered, the transvenous placement of caval interruptive devices is associated with lower morbidity and mortality rates as compared to the direct surgical approches.

LONG-TERM MANAGEMENT

After completion of an initial course of heparin therapy, patients should be maintained on long term anticoagulant therapy with either coumadin or SQ heparin for 4 to 6 months after hospital discharge. As can be seen from Figure 6, maintenance on anticoagulant therapy beyond this time interval is seldom warranted as potential benefits of therapy are outweighed by the risk of bleeding complications. An exception to the latter statement are those patients with continued high risk for pulmonary embolism due to the persistence of known predisposing factors, and those with a prior history of thromboembolism. Such patients may require more prolonged or even life-time anticoagulation.

Figure 6



Rate of recurrent thromboembolic events after hospital discharge in patients who did (•) or did not (x) receive outpatient anticoagulation (drawn from previously published data[illegible])

Chest 86(1):109, 1984

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HEMOPTYSIS

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INTRODUCTION

Massive hemoptysis is an uncommon pulmonary condition that mandates rapid stabilization and treatment of the afflicted patient. It has been defined by various authors as 100 - 600cc per day of blood loss into the tracheobronchial tree (1-4). Mortality is directly proportional to three factors: 1) rate of blood loss, 2) volume of blood loss, and 3) the patient's underlying medical condition (see table 1) (2,5). Massive hemoptysis is most often associated with inflammatory lung disease, with active and inactive tuberculosis making up a large portion of the cases (6). The source of the bleeding is usually from the bronchial circulation (7).

Optimal management involves a team approach which includes the medical intensivist, pulmonologist, radiologist, anesthesiologist, and thoracic surgeon. The greatest immediate risk to the patient is asphyxia (3). Temporizing measures that have been successfully used to control bleeding in the airway include selective intubation of a mainstem bronchus, endobronchial tamponade, IV pitressin, and bronchial artery embolization (8). If the site of bleeding can be localized by bronchoscopy and the patient has adequate pulmonary reserve, surgical resection should be accomplished (9).

ETIOLOGY

Massive hemoptysis may be caused by a variety of pulmonary insults both chronic and acute. Table 2 lists the causes of massive hemoptysis in relation to their frequency of occurrence. The distribution of cases has changed little in the past 20 years (see Table 3).

It should be noted that it is unusual for bronchogenic carcinoma to cause massive hemoptysis. Although 50% of patients with lung cancer will experience hemoptysis during the course of their disease, it is generally minor (10).

Causes of hemoptysis other than inflammatory lung disease vary widely in etiology and constitute a small percentage of cases. A representative sampling is included under the category of uncommon causes of massive hemoptysis listed in Table II. Massive hemoptysis related to alveolar hemorrhage syndromes and Swan-Ganz catheterization may require special management (see section Special Considerations).

Why is inflammatory lung disease associated with massive hemoptysis? Massive hemoptysis is generally associated with bronchial arterial bleeding (7). Inflammatory pulmonary lesions are hypervascular and result in the development of bronchial arterial collaterals which tend to dilate (8). If the tissue overlying these vessels is eroded secondary to chronic or acute irritation or trauma, pulmonary hemorrhage will ensue. In the setting of diffuse pulmonary disease, particularly associated with pleural disease, non-bronchial systemic vessels may be the source of hemorrhage (11). The pulmonary arterial circulation is generally not the source of massive hemoptysis unless a Rasmussin aneurysm or AVM is the cause of hemorrhage (7).

HISTORY

In the setting of massive hemoptysis, a directed, abbreviated history can provide valuable information regarding the cause of hemorrhage. This may result in the expeditious institution of life-saving therapy. The interviewer should attempt to localize the source, estimate the quantity and determine the onset, duration, and character of the blood coughed up. In addition, conditions associated with hemoptysis should be identified (see Table 4).

Although bronchogenic carcinoma is an infrequent cause of massive hemoptysis, the diagnosis must be entertained in patients over the age of forty who are cigarette smokers (1). In reality many patients have multiple risk factors by history alone. They may have a history of a positive PPD or an exposure to TB coexistent with COPD and chronic bronchitis. The duration of hemoptysis may be helpful, with long standing minor hemoptysis favoring bronchiectasis or bronchogenic carcinoma.

Some patients may be able to localize the site of bleeding to a particular side of the chest. This may be helpful in positioning the patient to minimize aspiration. However, one study by Kinasewitz et al demonstrated that 51 out of 67 patients were unable to correctly identify the site of a cough stimulus administered via the bronchoscope (12). Information obtained from the patient regarding the site of bleeding should be kept in its proper perspective.

Many patients find it difficult to identify the organ system responsible for bleeding, let alone the hemithorax. Careful questioning regarding nausea, hematemesis, melena or prior gastrointestinal disease may be helpful. The appearance may aid in diagnosing the site of hemorrhage. In hemoptysis bright red blood is mixed with frothy sputum and the specimen should be devoid of food particles. The suctioning of blood or hemoccult positive material from the stomach via a nasogastric tube may not reliably differentiate hematemesis from hemoptysis, since some patients with hemoptysis, particularly women, will swallow coughed up blood. If the patient does swallow the blood, quantification of hemoptysis may be inaccurate.

The presence of purulent material in the sputum suggests bronchiectasis or lung abscess. A history of valvular heart disease suggests a diagnosis of mitral stenosis. The report of tearing chest pain prompts consideration of a ruptured aortic aneurysm. The presence of hematuria may point to a medication overdose or interaction, or the presence of an alveolar hemorrhage syndrome.

PHYSICAL EXAM

Physical findings that may be important in the patient with massive hemoptysis are listed in Table 5. As mentioned previously, the more debilitated the patient the higher the risk of death, primarily from aspiration. Obtunded patients with inadequate cough reflex may suffer dire consequences after aspirating small amounts of blood. While it is unusual for patients to be hypovolemic as a result of hemoptysis, a small percentage of patients in whom the airway is adequately managed may risk exsanguination (13). Also, if chronically ill, patients with hemoptysis may present to the hospital hypovolemic secondary to decreased fluid intake. It is therefore prudent to assess these patients' volume status.

A careful head and neck exam is essential in the workup of hemoptysis. Examination of the nose, oropharynx and larynx may reveal an upper respiratory tract source. Ulceration of the nasal septum may suggest Wegner's granulomatosis. Telangiectasia on the lips or buccal mucosa is associated with Rendu-Osler-Weber disease. Scalene, cervical or supraclavicular adenopathy suggests bronchogenic carcinoma.

On chest exam, localized rales, wheezes or rhonchi may point to the site of pulmonary hemorrhage or indicate the need to institute bronchodilator therapy. Mitral stenosis may be appreciated on cardiac exam. Evidence of chest trauma with or without rib fracture suggests pulmonary contusion.

If petechiae or ecchymoses are found on examination of the extremities, a bleeding disorder, intrinsic (e.g. autoimmune) or extrinsic (e.g. drug-induced), may be present. Clubbing is seen in a variety of pulmonary and non-pulmonary disorders including bronchogenic carcinoma and bronchiectasis.

LABORATORY

Routine preoperative laboratory studies should be obtained on all patients in anticipation of thoracotomy. These studies include a complete blood count, prothrombin time, partial thromboplastin time, serum electrolytes, blood urea nitrogen, serum creatinine and urinalysis. In addition, a sputum sample should be examined for bacteria, acid fast bacilli (AFB) and fungal organisms. Sputum cultures for bacteria, AFB and fungus should be sent to the laboratory along with sputum for cytology. If the patient's PPD status is unknown, an intermediate strength PPD should be placed. If there is sufficient suspicion for coccidioidomycosis or histoplasmosis, appropriate skin tests and serologies should be ordered.

A chest x-ray should be obtained on all patients, preferably a PA and lateral film. The radiograph may yield specific information such as: 1) a new alveolar infiltrate representing pulmonary hemorrhage, 2) a pulmonary mass or cavity, 3) evidence of lung abscess, 4) an enlarged left atrium with Kerley B lines suggesting mitral stenosis, 5) a lobulated mass suggestive of an arteriovenous malformation. One must keep in mind, however, that an abnormality on the chest x-ray may not correspond to the site of bleeding (14).

MANAGEMENT

The management of massive hemoptysis may be subdivided into two distinct categories. The first involves stabilization of the patient and notification of the appropriate consultants. The second category involves attempting to establish a definite etiology of the hemoptysis and instituting the proper therapy.

Maintenance of the patient's airway is of prime importance. The task may be considerable if the rate of bleeding is brisk. Table 7 outlines the measures that should be instituted or considered in the initial phase of management. Supplemental oxygen should be given to all patients with massive hemoptysis; as blood fills the tracheobronchial tree, ventilation perfusion mismatch worsens. Two large bore IV's should be placed to allow access for crystalloid and colloid support, administration of IV medication, and to prepare the patient for possible surgery. Six units of blood should be typed and crossmatched. Cough should be suppressed but not abolished with 30-60mg of codeine I.M. every six hours. Excessive chest manipulation such as chest percussion and spirometry should be avoided. The risk of spirometry provoking bleeding is probably small but in the presence of massive hemoptysis ventilatory reserve may be significantly underestimated therefore making the test questionable in value (2). The patient should be positioned with the presumed bleeding side down in a lateral decubitus Trendelenburg position. This will lessen spill over into the "good lung" and promote drainage of the airway. If bronchospasm or purulent sputum has been identified, appropriate IV antibiotics and/or bronchodilators should be started. Adequate suction and a large bore endotracheal tube (8.0-9.0mm) with a laryngoscope should be present at the bedside.

If prior to bronchoscopy the bleeding becomes so rapid that respiratory arrest is imminent, the following measures may be attempted. The endotracheal tube can be advanced until breath sounds are no longer heard over the left side of the chest (normally the right mainstem bronchus lies in the same axis as the trachea). If the patient is not bleeding from this side the cuff can be inflated and the patient ventilated with the airway protected. If the patient is bleeding from the side that is selectively intubated, a Foley catheter can be placed in the airway and inflated. The endotracheal tube can then be slowly withdrawn until breath sounds are once again present on the left (15). Tube placement should be verified by a chest radiograph. One should also consider the use of IV vasopressin (0.2-0.3 u/min) in this setting. This has been reported to be an effective temporizing measure in the setting of massive hemoptysis (16).

Use of a double lumen tube, Carlens or Robertshaw, offers no significant advantage over selective intubation. Placement of these tubes requires experienced personnel. In addition the small lumen of the Carlens tube makes suctioning difficult (5,17). If mechanical ventilation is needed, some authors have suggested that PEEP may be therapeutic by providing a measure of tamponade to the site of hemorrhage via the increase in intrathoracic pressure (8). This therapy should be used with caution. PEEP may increase the risk of hypotension and barotrauma associated with mechanical ventilation, particularly in patients with COPD. Once the patient has been stabilized, attempts to identify the site of bleeding and institute definitive therapy must be made. Figure 1 is an algorithm illustrating this approach.

Bronchoscopy is the procedure of choice for the diagnosis of the site of bleeding (9). Both rigid bronchoscopy and flexible fiberoptic bronchoscopy have been used successfully with similar diagnostic yields (3). The choice of which bronchoscope to use will depend on the rate of bleeding and the personal experience of the pulmonary and thoracic surgery consultants. If bleeding is considerable and ongoing, the patient is best handled in the operating room with rigid bronchoscopy. The rigid bronchoscope provides better suction and the capability to ventilate the patient. If bleeding is less severe, a large channel flexible bronchoscope may be used, such as the Olympus T1. This bronchoscope will pass freely through an endotracheal tube that is 8.0mm or larger. The flexible bronchoscope offers the advantage of direct visualization of the upper lobes and the opportunity to place a four French Fogarty catheter in a segmental or subsegmental bronchus if the bleeding site is identified (6). Segmental lavage with iced isotonic saline may aid in identifying and controlling the hemorrhage. This method has been used successfully with both rigid and flexible bronchoscopy (6,18). Topical epinephrine (1:20,000 dilution) may be helpful if an endobronchial lesion such as an adenoma is the source of hemorrhage.

Once the site of bleeding has been localized and controlled, a decision regarding more definitive therapy must be made. If the patient is an operative candidate pulmonary resection should be performed. Criteria for inoperability include: 1) FVC or FEV1 of <40% predicted, 2) unresectable carcinoma, and 3) bilateral pulmonary disease with inability to localize the site of bleeding by bronchoscopy (9).

If the site of bleeding cannot be localized and the bleeding has stopped at the time of bronchoscopy, observation with serial hematocrits, chest x-ray and ABGs in conjunction with repeat bronchoscopy may be most prudent. If, on the other hand, the site of bleeding cannot be localized and the patient is still actively bleeding, bronchial arteriography may be attempted. Angiographic findings that implicate a particular site as the source of bleeding are: 1) localized hyperemia, 2) massive systemic to pulmonary artery or vein shunt, 3) pericavity vascularity, 4) extravasation of contrast medium (a rare finding) (19). The roles of chest CT and nuclear medicine studies (Tc-99m sulfur colloid and Tc-99m labeled red blood cells) in localizing bleeding are uncertain at the present time (20-22).

In patients who are not surgical candidates and who continue to bleed, bronchial artery embolization should be attempted. If Gelfoam is used as the material for embolization and care is taken not to embolize the spinal artery, complications are minimal (19). Uflacker's series of 75 patients reported immediate control of hemoptysis in 64 patients (76.6%) and a recurrence rate of 21.7% during the followup period ranging from 1-47 months (19). If no abnormalities are identified on the bronchial arteriogram the non-bronchial systemic vessels should be investigated to identify the source of bleeding (11). If bleeding persists after a thorough investigation of the bronchial and non-bronchial systemic arteries with embolization where appropriate, the pulmonary circulation should be studied.

SPECIAL CONSIDERATIONS

Mitral Stenosis

The infrequent patient who presents with massive hemoptysis secondary to mitral stenosis should undergo mitral commissurotomy or mitral valve replacement early in his hospital course. Non-surgical management of these patients has uniformly led to a poor outcome (24).

Alveolar Hemorrhage Syndromes

Occasionally alveolar hemorrhage syndromes present with massive hemoptysis that is diffuse. Institution of extracorporeal membrane oxygenation may be life-saving in this situation, buying time until more conventional therapy (pheresis, steroids, Cytoxan) can take effect (25).

Cystic Fibrosis

More and more patients with cystic fibrosis are living into adulthood. Their frequent pulmonary infectious complications may be associated with hemoptysis which can be massive at times. The bilaterality of their disease coupled with uniformly poor pulmonary function mandates extremely conservative management of bleeding episodes. Thoracotomy should be reserved for patients with adequate pulmonary reserve whose bleeding cannot be controlled by endobronchial tamponade and/or bronchial arterial embolization (26).

Pulmonary Artery Catheters

Since its introduction in 1970, the pulmonary artery catheter has emerged as a common tool in managing patients in an intensive care setting. Along with its frequent use have come case reports of complications, many of which are life-threatening. By 1984 a total of 28 cases of pulmonary artery rupture had been reported in the literature with hemoptysis present in 23 of the 28 patients (27). This infrequent complication has a mortality of 45% (27). If pulmonary artery rupture occurs the following measures are suggested for management (27,28).

1. Anticoagulation should be reversed immediately.

2. The catheter should be kept in place and immediate embolization performed by means of an autologous clot.

3. If hemoptysis is persistent, the patient should be sedated and intubated to allow suctioning and ventilation of the uninvolved lung.

4. PEEP may be helpful if the patient is not hypovolemic.

5. If the bleeding continues prompt thoracotomy and wedge resection or lobectomy should be carried out.

6. If proper equipment is available, autotransfusion should be considered.

MORTALITY ACCORDING TO RATE OF BLEEDING

	Operable				Non Operable	
	Surgery		No Surgery			
	Patients	Died	Patients	Died	Patients	Died
600cc/4 hr	11	4 (36%)	6	6 (100%)	11	10 (91%)
600cc/4-16 hr	10	1 (10%)	3	1 (33%)	5	2 (40%)
600cc/16-48 hr	11	1 (9%)	0	0	10	0

Adapted from Crocco et al
Massive Hemoptysis
Arch Intern Med 1968 121:495

Table II

CAUSES OF MASSIVE HEMOPTYSIS

Common

- Tuberculosis
  - active
  - inactive
- Bronchiectasis
- Pulmonary Abscess
- Mycetoma

Less Common

- Bronchogenic Carcinoma
- Cystic Fibrosis

Uncommon

- Iatrogenic
  - drug related
  - procedure related
- Alveolar Hemorrhage Syndrome
- Cardiovascular Disease
  - congenital
  - acquired
- Bronchial Adenoma
- Metastatic Carcinoma
- Broncholithiasis
- Foreign Body Aspiration
- Pulmonary Contusion
- Dissecting Aortic Aneurysm

Table III

ETIOLOGY OF MASSIVE HEMOPTYSIS

	Number of Patients	Tuberculosis	Inflammatory Lung Disease	Cancer	Other
Pursel et al (1961)[1]	5	2	2		1
Amirana et al (1968)[29]	5	5			
Crocco et al (1968)[2]	67	49	13	5	
Smiddy and Elliott (1973)[35]	12		11		1
Gourin and Garzon (1974)[4]	62	45	11	2	4
Mattox and Guinn (1974)[30]	4	1	1	1	1
McCollum et al (1975)[31]	7	4	1	1	1
Saw et al (1976)[32]	10	6	3		1
Sehhat et al (1978)[33]	146	30	95	17	4
Conlan et al (1983)[18]	123	47	58	6	12
Bobrowitz et al (1983)[3]	15	12	2		1
TOTAL	456	201 (44%)	197 (43%)	32 (7%)	26 (5%)

Adapted from Imgrund et al. Clinical Diagnosis of Massive Hemoptysis Using the Fiberoptic Bronchoscope. Critical Care Medicine 1985 13:438

Table IV

KEY HISTORICAL POINTS

HPI

- Age of Patient
- Onset and Duration of Hemoptysis
- Source of Bleeding - Upper respiratory tract
  - Lower respiratory tract
  - Gastrointestinal tract
- Amount of Blood
- Characteristics of Sputum
- Associated Chest Pain/Trauma
- Smoking
- Medications
- T B Exposure

PMH

- Cardiopulmonary Disease
- Autoimmune Disease
- Blood Dyscrasia

ROS

- Nasal Symptoms
- Oropharyngeal Symptoms
- Laryngeal Symptoms
- G.I. Symptoms
- Hematuria

Table V

LABORATORY STUDIES

CBC

PT/PTT

Electrolytes, BUN, Creatinine

UA

Sputum - Smear and Culture for bacteria, acid fast bacilli, and fungus

Sputum Cytology

PPD (intermediate strength)

CXR

Table VI

IMPORTANT PHYSICAL FINDINGS

- General
  - Level of Consciousness
  - Orthostatic Changes
- Head and Neck
  - Ulceration of Nasal Septum
  - Telangiectasia
  - Oropharyngeal Lesion
  - Laryngeal Lesion
  - Adenopathy
- Chest
  - Chest Trauma/Rib Fracture
  - Localized Wheezes, Rales, Rhonchi
  - Diastolic Rumble/Opening Snap
- Extremities
  - Clubbing
  - Petechiae/Ecchymosis

Table VII

INITIAL MANAGEMENT OF MASSIVE HEMOPTYSIS

Oxygen

Two Large Bore IV's

Type and Cross Six Units of Blood

Cough Suppression

Proper Positioning - Slight Trendelenburg and lateral decubitus position (bleeding site down)

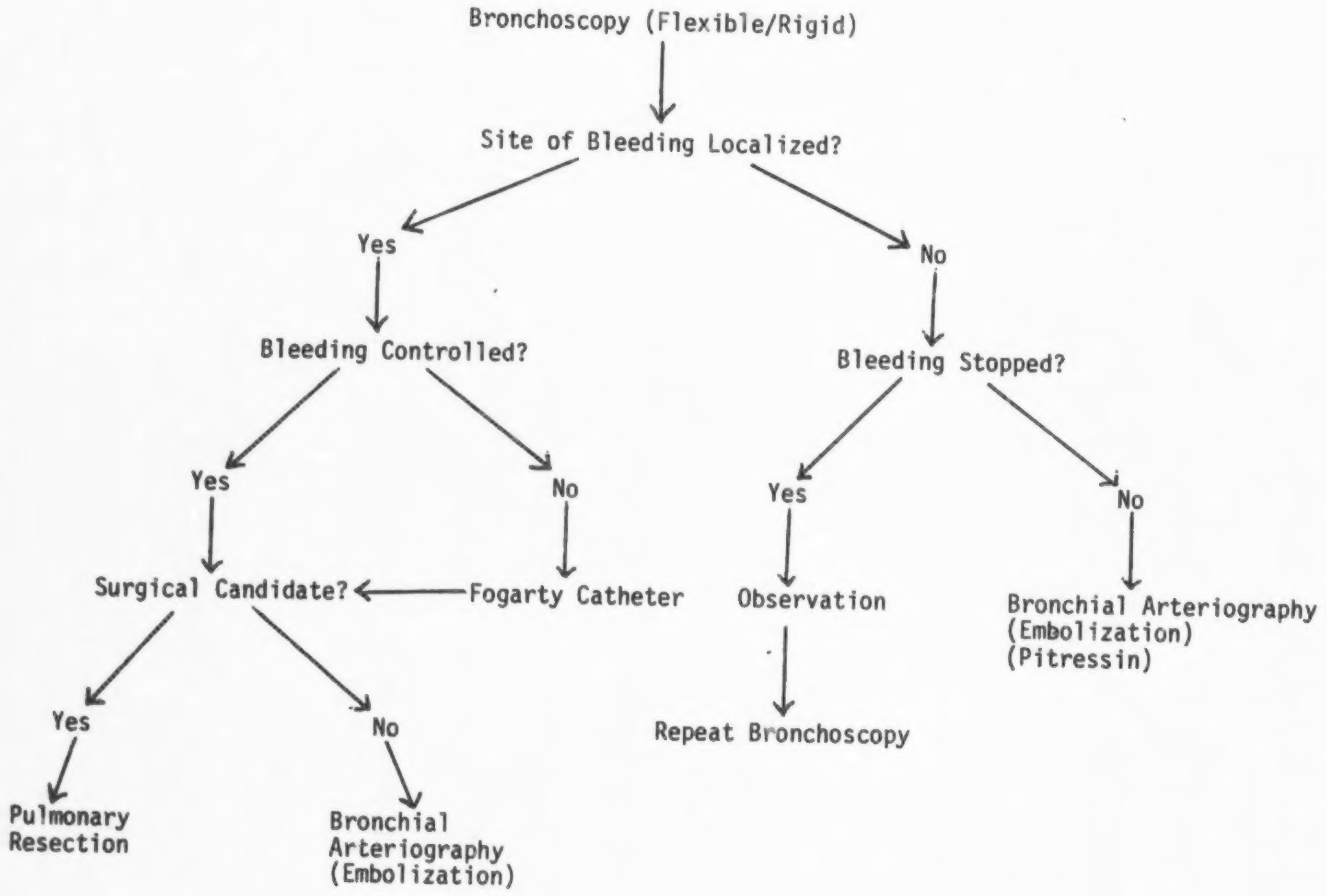
Antibiotics/Bronchodilators (if indicated)

Endotracheal Tube and Suction at Bedside

(Pitressin)

Figure 1

MANAGEMENT OF MASSIVE HEMOPTYSIS


Bronchoscopy (Flexible/Rigid)
Site of Bleeding Localized?
Yes
No
Bleeding Controlled?
Bleeding Stopped?
Yes
No
Yes
No
Surgical Candidate?
Fogarty Catheter
Observation
Bronchial Arteriography
(Embolization)
(Pitressin)
Yes
No
Repeat Bronchoscopy
Pulmonary
Resection
Bronchial
Arteriography
(Embolization)

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SOLITARY PULMONARY NODULE

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A solitary pulmonary nodule is defined as a rounded, discrete relatively smooth density less than 6 cm in diameter which is completely surrounded by normal lung parenchyma. Lesions with poorly defined borders or those larger than 6 cm are much more likely to be malignant (1). Lesions with satellite nodules or certain calcification patterns are more likely benign (1).

There are at least fifty pathologic processes which may present as a SPN (1). The only one of real concern to the clinician (and the patient) is the likelihood of malignancy. The incidence of malignancy varies from 40% in surgically oriented referral clinics (2) to about 3% if SPN is found on routine screening chest x-ray (3-5).

What to do with the SPN is somewhat controversial. Some authorities recommend following the nodule if the patient is less than 35 years old and surgical removal if the patient is 40 years of age or older. This appears simple enough but is probably too simplistic.

The first step is a good history and physical examination with emphasis on the following:

1. History or physical findings suggestive of a primary malignancy outside the lung.

2. Significant constitutional symptoms (most patients presenting with a SPN are asymptomatic, however).

3. Signs of metastatic disease (supraclavicular and cervical nodes, liver enlargement, etc.).

4. Risk factors for lung carcinoma (smoking, asbestos exposure, prior malignancy, etc.).

5. Present residence in or travel to areas where granulomatous disease would be likely (i.e. cocci, histo, etc.)

6. Risk factors which might complicate diagnostic procedures or thoracotomy.

7. Laboratory studies. A positive PPD or cocci skin test may be interesting but is rarely helpful in evaluating the individual patient. Sputum cultures for AFB or fungi are rarely positive but should be done anyway; they may be helpful,

particularly if the nodule is cavitary. The CBC may be abnormal, particularly with oat cell carcinoma where bone marrow involvement is frequent. Abnormal liver function tests may indicate occult liver involvement. Sputums for cytology are rarely helpful (less than 20% positive) but should be done since they are easily obtained without discomfort or risk to the patient.

The next and often most important step is to obtain old chest x-rays if possible. If it can be demonstrated that the lesion has been radiographically stable for two years it can be presumed benign; such patients should be followed with chest x-rays every six months. If the nodule enlarges the patient must be reassessed. (Even then, the lesion may be benign; for instance, histoplasmomas may enlarge over time, although calcium can usually be demonstrated by tomography.) Doubling times may be of help - doubling times of less than 6 weeks or greater than 18 months suggest benignity. Adenocarcinomas double in volume in about 6 months, squamous cell carcinomas in 3 months and small cell carcinomas in 1-2 months (6). (An increase in the radius of 1.26 times is two times the previous volume, and represents one doubling time.)

Tomographic study of the nodule should be considered. The lesion is presumed benign if it has laminar, central or stippled calcifications. Eccentric calcification may be due to a carcinoma engulfing a granuloma, although this is extremely rare; somewhat more common is the possibility of a scar carcinoma arising in an old granuloma. Tomograms may also show cavitation of the lesion, but this is no help in differentiation of benign and malignant lesions (infectious processes frequently cavitate; squamous cell carcinomas cavitate about 10% of the time, adenocarcinomas and large cell carcinomas much less, and oat cells never) (6).

Computed tomography (CT) of the chest will reveal about 30% more nodules than standard lung tomography (7); sometimes it demonstrates more nodules than one knows what to do with! At the present time, however, it usually provides no further information as to whether the lesion is benign or malignant. Siegelman (8) has advocated chest CT in the diagnostic evaluation of the SPN. He found that nodules with a CT number - a function of tissue density - greater than an arbitrary cut-off were invariably benign, correlating to deposition of calcium not visible on routine chest x-ray or tomography. Unfortunately, his work has not been reliably duplicated and must be considered a research tool, in large part because of the variability between scanners in calculating density numbers. Currently, there is a great deal of interest in the use of a "phantom", a synthetic "pulmonary nodule" which can be scanned by the CT as a density reference.

This may be of benefit in the future to help avoid thoracotomy for granulomatous disease (9). Current indications for chest CT include:

1. To evaluate the mediastinum.

2. To determine if a presumed metastatic nodule being considered for resection is indeed solitary.

3. To rule out pulmonary metastases in a patient with sarcoma of the extremity when amputation is considered.

Frequently, after all of the above are done, the patient is still left with an "indeterminate" nodule and more invasive studies must be undertaken. The initial step is usually fiberoptic bronchoscopy with biopsy and brushings. This is most usually successful with endobronchial lesions and lesions in the mid-lung field. Lesions far peripheral or close to the hilum that are not visualized endobronchially offer lower yield (close to hilum 30%, mid-lung 90%, peripheral 60%) (12,13). Lesions originating in the interstitial space (metastatic tumors and scar carcinoma) are less likely to be diagnosed by transbronchoscopic biopsy. If the patient meets the criteria for surgery (listed later), bronchoscopy is still indicated for three reasons:

1. To define anatomy and look for evidence or suggestion of non-resectability (tumor within 2 cm of the carina, compression from hilar or mediastinal nodes).

2. To rule out multicentric cancer (particularly in squamous cell carcinoma).

3. To rule out oat cell carcinoma (essentially a non-surgical lesion, although resection may be indicated for a small peripheral oat cell - this is debatable).

If a diagnosis is not obtained by bronchoscopy, then a transthoracic fine needle aspirate might be indicated. The needle is passed through the chest wall into the nodule under fluoroscopic control. Examination of the aspirated material is most helpful in ruling in malignancy, but granulomas have been diagnosed (not always reliably) by this technique. In good hands the fine needle aspirate has a false negative rate of about 10% (14); i.e., nodules ultimately proven to be cancer have benign aspirate cytology 10% of the time. Some institutions have used the fine needle aspirate in almost all patients with a solitary pulmonary nodule but our criteria are more rigid. This technique should be reserved for patients in whom the bronchoscopy is negative and (1) the lesion is highly suspicious for small cell carcinoma; (2) the patient has contraindications to surgery for medical reasons; (3) the patient has obvious metastatic disease (i.e. a brain metastasis), and only a tissue diagnosis is necessary; or (4) the patient has multiple nodules suspicious for metastatic disease and tissue diagnosis is needed.

The clinician must then decide whom to send for surgical resection. It must be recognized at the present time that surgery offers the only reasonable hope of cure in patients with non oat-cell lung cancer, so it is wise to err on the side of an aggressive approach. Candidates meeting the following criteria appear reasonable for thoracotomy:

1. Age over 35 years (below this age the risk of thoracotomy almost always exceeds the possibility of malignancy) (14).

2. (a) Previous films not available, or

(b) Previous films available, demonstrating a smaller or non-existent nodule, or

(c) Previous films available, but not old enough to demonstrate stability of the nodule over a 2 year period.

3. Lack of "benign" calcium in the lesion

4. General medical status adequate to undergo an operation.

The choice of a cervical mediastinal exploration or anterior mediastinal exploration (Chamberlain procedure) prior to definitive thoracotomy depends on several factors, including the size of the lesion, proximity to the hilum, cell type, and cardiopulmonary status (where evidence of unresectability may be important) (16,17).

The prognosis for the resected solitary pulmonary nodule which ultimately proves to be malignant is better than in most lung cancer, approaching 45% survival at 5 years in some series (18). Prognosis is also relatively good in patients with a nodule secondary to a previously treated extrathoracic malignancy; 20% of these patients may survive 5 years after resection (19).

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BRONCHOGENIC CARCINOMA

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INTRODUCTION

Bronchogenic carcinoma is now the major oncological problem in America, as measured by age adjusted death rates (1) (Figures 1 and 2). As of 1985, it has surpassed breast carcinoma as the most common cause of cancer deaths in females, and remains the most common cause of cancer deaths in males. This high death rate has resulted from both a rapidly rising incidence of the disease and the poor results of therapy (approximately 8-10% five year survival) (1,2,3).

ETIOLOGY AND EPIDEMIOLOGY

Referring to Figures 1 and 2, two questions arise. Why has there been such a marked increase in lung cancer death rates? Why is lung cancer now the most common cause of cancer deaths in females?

The first question was answered in the 1960s, when the Public Health Service prepared several reports clearly linking lung cancer to smoking (2). A dose-response relationship between cigarette smoking and lung cancer exists; average cigarette smokers have an approximate 10-fold increased risk for developing lung cancer and heavy smokers have at least a 20-fold increased risk. The risk is directly related to total exposure to cigarette smoke (hence the use of "pack years" to quantitate exposure). However, the risk does fall gradually in ex-smokers, perhaps reaching non-smoker levels after 10 to 15 years.

The increased death rate from lung cancer in males is related to the increase in cigarette smoking that began in the early 20th century. Females began to smoke more cigarettes in the 1940s and 1950s, and death rates for women began to climb in the 1960s (1).

It appears that all cell types of lung cancer are linked to cigarette smoking, though some more strongly than others. The VA hospital in East Orange, NJ, reviewed the smoking histories of 662 men who had died from lung cancer and had undergone post-mortem examination (5). Only six subjects had never smoked; all of these had adenocarcinoma (altogether there were 167 adenocarcinomas). Table 1 shows the Mayo Clinic data on cell types and smoking history; unlike the VA study, females are included (3). Here again, all cell types are linked to smoking, adenocarcinoma less strongly in females.

Besides cigarette smoke, several other agents are associated with increased risk for developing lung cancer (2):

1. The overall death rate from lung cancer for pipe and cigar smokers is higher than non-smokers, though not as high as cigarette smokers.

2. Asbestos is the most clearly documented industrial agent associated with lung cancer. This effect is most clearly seen among smokers.

3. A thoroughly documented association exists among uranium miners between lung cancer and exposure to irradiation.

4. Other industrial agents associated with increased risk for lung cancer include chromates, nickel, and arsenic.

5. There is an association between lung scars and lung cancer, as seen in higher than predicted rates of lung cancer in patients with "scleroderma lung", idiopathic pulmonary fibrosis, and (possibly) TB.

6. It is not clear whether air pollution in general plays any significant role in the etiology of lung cancer.

HISTOLOGICAL GROUPS OF LUNG CANCER

There are several histologic classifications of lung cancer. The AFIP divides lung cancer into five groups: 1) squamous cell, 2) adenocarcinoma (including bronchoalveolar subtype), 3) large cell carcinoma, 4) combined squamous cell and adenocarcinoma, and 5) small cell carcinoma (50).

Recent theories of lung cancer pathogenesis state that all lung cancers arise from a common lung stem cell. Small cell carcinoma is poorly differentiated and extremely aggressive, while more differentiated tumors such as squamous cell and adenocarcinoma demonstrate slower growth rates (51,58).

Cell type is important in planning therapy and estimating prognosis. X-ray presentation, endobronchial location and associated syndromes vary with each cell type.

Table 2 lists cell types in several large series of patients (3,5,6,7). Squamous cell (or epidermoid) carcinoma is the most common with adenocarcinoma second. The incidence of adenocarcinoma is rising faster than that of other cell types (3). Next in frequency is small cell followed by large cell undifferentiated carcinoma. Tumors are not always homogeneous, so final cell type will depend on how much tissue is sampled and on the reviewing pathologist.

Table 3 is an abbreviated version of Mayo clinic data on 600 patients with lung cancer who had abnormal chest x-rays at the time of presentation (8). Under each cell type is the percentage of patients with the specified abnormality. (This table will be used in the following discussion.)

Table 4 contains the same data rearranged to show which cell types were associated with each roentgenographic presentation.

Squamous Cell Carcinoma (2,3,8)

When arising centrally squamous cell carcinoma tends to grow into the bronchial lumen, causing obstruction. It is the most common cell type to cavitate (10%). It has the lowest overall incidence of metastases but the highest incidence of solitary extrathoracic metastasis. It has the best prognosis of all cell types at any given stage of disease.

Adenocarcinoma (2,3,8)

Adenocarcinoma arises more peripherally than squamous or small cell, most frequently appearing as a mass surrounded by lung parenchyma (71%) on chest x-ray. In some series, (not Mayo's), it is the most frequent cell type to have an associated pleural effusion (10%) and the least likely type to cause obstruction. It is the most frequent cell type found in "scar carcinoma".

If a solitary pulmonary nodule is resected and turns out to be adenocarcinoma, should an extrathoracic primary be sought? If the history, physical exam, and routine lab do not point to another tumor, no further search should be undertaken.

Bronchoalveolar cell carcinoma, a sub-type of adenocarcinoma, has several distinguishing features. The tumor seems to arise peripherally, and the cells may spread endobronchially and line the alveolar spaces (2). It has a great variety of x-ray presentations, most commonly as a segmental or lobar alveolar infiltrate, but also as a patchy infiltrate, a mass, or diffuse disease involving both lungs. These patients may produce copious amounts of mucoid sputum (2); although bronchorrhea is a classic presentation, it is actually unusual.

Small Cell Carcinoma

This tumor usually arises centrally (8), but often grows along the bronchial wall submucosally rather than intraluminally (3). Thus, it may be harder to diagnose by bronchoscopy than a central squamous cell, and may cause obstruction of a bronchus by extrinsic compression. It almost never cavitates (8).

It is virtually always metastatic at time of presentation, and thus is usually not amenable to surgery (2,3,9,10). An iliac crest bone marrow biopsy will be positive for tumor in 40% of the cases at presentation, providing an alternative to bronchoscopy for making the diagnosis (11,12). Another series found small cell carcinoma in the liver of 8 of 19 cases who underwent peritoneoscopy and liver biopsy (13).

It is the most common type of lung cancer to be associated with paraneoplastic syndromes. The most rapid growing bronchogenic carcinoma, it is the only one regularly responsive to chemotherapy (9).

Large Cell Carcinoma

This cell type is often a "wastebasket" term for tumors which are not clearly either squamous cell or adenocarcinoma, and tends to be used when only small amounts of the tumor are available for pathologic study. It usually appears as a large peripheral or central mass, and may involve the mediastinum grossly at presentation (as can the other anaplastic cell type, small cell) (8).

SIGNS AND SYMPTOMS (2,3)

The symptoms and physical findings produced by lung cancer can be divided into five groups (2,3): 1) local effects of the tumor, 2) problems secondary to intrathoracic spread, 3) manifestations of distant metastases, 4) non-specific systemic symptoms unrelated to tumor location, and 5) paraneoplastic syndromes. About 25% of patients are asymptomatic at presentation (3).

Table 5 is a list of initial symptoms of 2,000 patients with lung cancer (2).

Local symptoms include cough, sputum production, dyspnea, and wheezing. Of course, these symptoms are common in cigarette smokers without lung cancer, and an increase in cough may not always prompt a chest x-ray in this population. Hemoptysis is more ominous and always deserves a chest x-ray. Sometimes these symptoms will be more striking, as when endobronchial tumor leads to bronchial obstruction and pneumonitis.

The tumor may spread in any direction in the thorax. Chest pain often represents parietal pleural (or deeper chest wall) involvement. A pleural effusion is a bad prognostic sign, whether caused by pleural malignancy, bronchial obstruction (atelectasis or para-pneumonic effusion) or lymphatic obstruction. There are numerous structures in the mediastinum which may be involved: left recurrent laryngeal nerve-(hoarseness); either phrenic nerve-(dyspnea); SVC syndrome; esophagus-(dysphagia); pericardium-(effusion and tamponade). An upper lobe tumor at the thoracic inlet may involve several structures (brachial plexus, sympathetic chain, adjacent ribs and vertebrae), producing the Pancoast syndrome; i.e. pain in the shoulder and ulnar nerve distribution of the arm, associated with Horner's syndrome.

Table 5 shows the most common sites for metastases: lymph nodes, bone, liver and brain. The adrenal glands are a frequent site for metastases but adrenal failure resulting from tumor replacement is rare.

Non-specific systemic symptoms, such as weight loss, fatigue, anorexia, and fever may occur without demonstrable tumor metastases, and are bad prognostic signs; their etiology is unclear.

Paraneoplastic syndromes are non-metastatic effects of a cancer on parts of the body not involved with the primary tumor. These effects are felt to be mediated by humoral substances secreted by the tumor, although these substances have not been identified in all instances. Table 7 lists some of the identified hormonal peptides secreted by cancers, and the most commonly associated cell types.

All lung cancers actively secrete hormonal peptides, but many of these hormones are not in a metabolically active form.

Therapy of paraneoplastic syndromes is primarily aimed at therapy of the underlying malignancy, however some syndromes will require special treatment:

1. Cushings syndrome (Ectopic ACTH) - These patients may present with weakness, polyuria, polydipsia, and mental confusion. Hypokalemic alkalosis is present and may be the only presenting manifestation. High levels of circulating cortisol are associated with a worse prognosis and may hasten metastatic spread. If the primary tumor is not amenable to direct therapy, then aminoglutethimide or metyrapone may be used to decrease steroidogenesis. 1, a-Dichloro-2-(O-chlorophenyl)-2-(P-chlorophenyl) ethane, (O, p'DDD), has been used, but has a slow onset of action and has severe gastric side effects.

2. Antidiuretic hormone (ADH) syndrome - This syndrome commonly seen with oat cell carcinoma causes water intoxication, marked hyponatremia, and low serum osmolality with an inappropriately elevated urine osmolality, which may result in cerebral edema. Patients may respond to water restriction

alone, but another effective treatment is demeclocycline (13 to 15mg/kg/day) in two divided doses. This produces a mild reversible nephrogenic diabetes insipidus. Hypertonic saline should only be used in cases of extreme electrolyte imbalance.

3. Hypertrophic pulmonary osteoarthropathy (HPO) - This syndrome consists of clubbing of the fingers and pains in the wrists, ankles, or knees associated with pannus-like proliferation of synovial tissue. Although a growth hormone-like substance is suspected, measured growth hormone levels do not correlate with disease activity. Patients have variable responses to anti-inflammatory medication. The syndrome can resolve completely with excision of the tumor. Although clubbing accompanies HPO, it can also occur by itself in association with lung cancer.

4. Eaton-Lambert syndrome - This myasthenia-like syndrome causes progressive weakness of pelvic and shoulder girdle musculature primarily. This syndrome is most commonly associated with oat cell carcinoma. Unlike myasthenia gravis, repetitive muscle stimulation results in an increase in strength, termed paradoxical potentiation. These patients are ultrasensitive to curare-like agents. Guanidine hydrochloride (25-35 mg/kg/day in divided doses) may help reverse symptoms.

5. Hypercalcemia (ectopic PTH) - Both ectopic PTH and ectopic prostaglandins have been associated with hypercalcemia. Diffuse bone metastases must also be considered when hypercalcemia occurs with lung malignancies. Large amounts of circulating PTH can be found in many lung cancers, but usually consist of a non-cleaved "big PTH" which is not metabolically active. Clinically significant ectopic PTH production is most commonly seen with squamous cell carcinomas. Therapy includes hydration and furosemide administration. Some patients may require treatment with mithramycin or calcitonin. Indomethacin may be effective in blocking hypercalcemia induced by prostaglandins.

DIAGNOSIS

Several methods are available for providing histological and/or cytological specimens in the patient with suspected lung cancer.

1. Flexible fiberoptic bronchoscopy is the most frequently used diagnostic procedure. Zavala has reported a yield of 94% in endoscopically visible lung cancer, and 71% in peripheral lesions using fluoroscopy (14).

Fiberoptic bronchoscopy can also provide information on endobronchial extent of tumor (important in staging) and help rule out a synchronous second primary.

2. Four sputum specimens for cytologic examination have been reported to make the diagnosis in 80% of central and 50% of peripheral carcinomas (4), although these figures may be too high. Unfortunately, "malignant" sputum cytology does not identify specific cell type in many cases. With the exception of oat cell carcinoma, or with known distant metastasis, positive sputum cytology does not alleviate the need for bronchoscopy to rule out second primary tumors and to define endobronchial extent.

3. If pleural effusion is present, pleural biopsy and pleural fluid cytology (3 thoracenteses if necessary) may have a 90% yield for malignancy (15). It is important to remember, however, that not all effusions associated with lung cancer are due to malignant pleural invasion; 5% are from non-malignant causes, and a larger percentage are caused by mediastinal node involvement which while usually denoting unresectability is associated with negative cytology.

4. Suspicious palpable lymph nodes should be biopsied, or a fine needle aspiration should be obtained. Eighty percent of enlarged scalene nodes will be positive for tumor (2).

5. Fine needle aspiration of the lung mass in the best hands is 85-95% sensitive for diagnosing carcinoma as long as cytopathology support is available. However, up to 24% of procedures may be complicated by pneumothorax (16,17). Of these almost half require chest tubes.

6. Posterior iliac crest bone marrow aspirate and biopsy will be positive in over 40% of small cell carcinomas (11,12).

7. In some cases the diagnosis will not be made until mediastinal exploration or thoracotomy (2).

RESECTABILITY AND STAGING

Staging refers to the process of determining the extent of a tumor and its spread. The principal reason for staging lung cancer is to determine whether or not the tumor can be removed surgically in hope of cure. The following criteria make a tumor unresectable (2,18,19,20,21).

1. Small cell carcinoma (except in the rare case of a small peripheral tumor, which many centers consider a surgical lesion).

2. Distant metastases (liver, brain, bone, etc.)

3. Certain regional nodal metastases: supra-clavicular, contralateral mediastinal/hilar.

4. Invasion of certain mediastinal structures: esophagus, central blood vessels, and pericardium. Assessing resectability in this setting involves surgical judgment if these findings are first noted at thoracotomy.

5. Endobronchial growth to within 2 cm of the main carina. A surgical decision as to whether or not a successful pneumonectomy can be performed is required.

6. Involvement of mediastinal nodes on the ipsilateral side probably implies unresectability. However, if the cell type is squamous, the nodes are relatively peripheral, and no extension through the capsule is noted, a resection may be attempted (controversial).

7. Diaphragmatic, chest wall, or parietal pleural extension (including a malignant pleural effusion). Exceptions include some tumors causing the Pancoast syndrome, and those parenchymal tumors extending to the chest wall which can be excised via an *en bloc* chest wall resection.

8. Involvement of left recurrent laryngeal nerve or either phrenic nerve (especially right side) if associated with a central tumor. Some surgeons may be willing to look at these cases in hope that the tumor or involved node is only compressing but not invading the nerve, but this is extremely rare.

At presentation, approximately 50% of tumors have distant metastases (extensive disease), 30% have some form of intrathoracic or regional spread, and 20% are apparently localized (22). If the tumor is non-small cell, the next step in staging is to investigate for distant metastases.

Currently, the following approach is widely advocated in locating distant metastases (3,18,23,24). A careful history and physical are performed, including a neurological examination. CBC and liver function tests are performed. If positive findings point to an organ abnormality (liver, bone or brain), then a radionuclide scan of that organ is obtained. In the absence of any positive findings, no routine scanning is necessary because the incidence of clinically silent metastases detected only by nuclear medicine scanning is low.

There are some physicians who do not agree with this viewpoint and advise various routine nuclear medicine studies (19). Since many of the sources do not cite hard data to support their claims, one cannot strongly disagree with even "shotgun scanning". The final answer to this question is not available. However, the literature has good studies which lend support to selective use of scanning (25,26).

1. UC San Diego did multiorgan scans in 52 patients with "operable bronchogenic carcinoma"..."patients who had obvious metastatic disease were exluded" (2). An internal medicine housestaff did the history and physical exam, and routine lab studies were obtained. In the 153 scans performed, 16 of 17 positive scans in patients with normal clinical findings were false positive. Only one scan (a bone scan) of 131 scans in patients with no evidence of metastases on clinical evaluation was true positive.

2. Walter Reed Medical Center studied 225 patients with bronchogenic carcinoma using multi-organ scans (liver, brain, bone) (26). All patients free of clinical findings had negative liver and brain scans. Positive bone scans occurred in 4 of 49 (8%) patients without clinical abnormalities. Follow-up in those 4 patients showed that 2 of 3 who underwent pulmonary resections remained free of disease 12 and 18 months postop, suggesting that the scan results were false positive. The fourth patient had small cell carcinoma. They concluded that liver, brain and bone scanning is indicated only in patients suspected of having metastatic disease on the basis of clinical or laboratory data.

Table 6 lists the findings which should raise suspicion of metastatic disease. If any of these is positive, the patient should have all three scans. This differs from the "standard" approach which relies on "organ specific" findings, e.g., a patient with headaches gets a brain scan only.

The next step in determining resectability is evaluation for intrathoracic spread and is discussed in depth in the following chapter.

OPERABILITY

Operability refers to the patient's ability to survive the (hopefully) curative surgery (4). There are several aspects to be considered in the pre-operative assessment of patients with presumably resectable non-small cell bronchogenic carcinoma.

The population of patients developing lung cancer is a subset of the cigarette smoking population (95% of the time). Consequently, there is a very high prevalence of COPD in patients with lung cancer. Recent data suggests that smokers with ventilatory obstruction are at greater risk for lung cancer than are smokers without obstruction (63). Impaired pulmonary function increases risks and complications of most major surgical procedures performed under general anesthesia (29). Thoracotomy with pulmonary resection (either lobectomy or pneumonectomy) will almost always reduce pulmonary reserve by removing lung parenchyma, further increasing the risk of surgery in a COPD patient.

Since it is not always possible to judge the intrathoracic extent of tumor preoperatively, a patient should be prepared preoperatively to undergo pneumonectomy (30). Simple criteria have been developed to predict a patient's post-pneumonectomy lung function (30). Using these criteria, operative mortality can be kept within acceptable limits and "curative" resection will not result in "respiratory cripples" (30). The following tests should be applicable to most patients:

1. Arterial blood gases - Hypercapnia generally contraindicates pulmonary resection (21). Hypoxemia may not, since PO_2 may improve when the most diseased portion of lung is removed, and since supplemental oxygen is readily available anyway.

2. Spirometry - it is felt that a patient should have a postop FEV_1 >800cc to avoid becoming a respiratory cripple (32). A preop FEV_1 >2 liters is considered sufficient, assuming no more than half the ventilatory capacity will be removed with pneumonectomy (31).

3. Lung Scan - Since it is likely that the diseased lung contributes less than half to the FEV_1, a resection on a patient with less than a 2 liter FEV_1 is possible if differential lung function tests predict an acceptable post-pneumonectomy FEV_1. By doing a routine macroaggregated albumin perfusion scan and recording the number of counts over each lung it is possible to predict post-pneumonectomy FEV_1 (30,31,32). In performing pneumonectomy on 33 high-risk patients with FEV_1 less than 2 liters, the Gainesville group found a 15% peri-operative mortality using these criteria (30). In long term follow-up of 38 such patients, there was information on cause of death in 29; only 5 died of respiratory failure after pneumonectomy (20 died with metastases) (31). A perfusion scan alone is just as good as a ventilation scan or combined ventilation-perfusion scan (33,34). A complete discussion of pulmonary function evaluation in lung resection is found in the chapter, "Pulmonary Preoperative Evaluation".

THERAPY FOR NON-SMALL CELL BRONCHOGENIC CARCINOMA

It is generally accepted that surgical resection is the only reasonable hope of cure for non-small cell bronchogenic carcinoma (2,3,4). Much of this discussion has been directed towards identifying which patients are candidates for curative resection. What kind of results can be expected in "curative surgery", in which all gross tumor has been removed?

The most representative figures for our patient population are probably those published by Stanford et al (6). In a review of Armed Forces Central Medical Registry Data, they found 1,027 cases of resection for cure. The five year survival in this group was 48.8%. As the article points out, these results are relatively good compared to most other large series (greater than 500 patients) which had 29-41% five year survival in patients who underwent what appeared to be curative surgery. The major factor exerting an adverse effect on survival in Stanford's review was the presence of involved nodes in the surgical specimen.

Are there any alternatives to surgery in patients with localized disease? Specifically, what can be done for a patient with apparently localized (hence resectable) tumor who is not fit for surgery (inoperable)? Since chemotherapy seems to be ineffective, radiotherapy offers the only chance of cure and/or increased survival. Use of radiotherapy in these cases was the subject of back to back editorials, one pro (35) and the other con (36). There was agreement that radiation can relieve specific symptoms, and that radiation is ineffective in prolonged survival in patients with distant metastases or intrathoracic spread (malignant effusion, nerve involvement, etc.). Advocates of immediate treatment of asymptomatic patients with local disease cite studies with 11-26% two year survival and 6-9% five year survival on average (35). Opponents have pointed out that these studies are mostly non-random and used historical controls, thus concluding that "at this time, there remain serious questions whether radiotherapy of asymptomatic patients with bronchogenic carcinoma is appropriate" (36).

Radiotherapy is useful to relieve symptoms in patients with limited or extensive disease. One large series (all cell types) found the following symptomatic response rates (37): hemoptysis 84%, arm and shoulder pain 73%, chest pain 61%, atelectasis 23%, superior vena cava syndrome 86%, vocal cord paralysis 6%, and dyspnea 60%. It is very effective in the treatment of cerebral and bony metastases.

THERAPY FOR SMALL CELL CARCINOMA

Small cell carcinoma differs from other bronchogenic carcinomas in several ways. From a practical standpoint, this is most evident in the choice of treatment modalities

Small cell carcinoma patients are stratified into limited or extensive disease (9). Thirty percent of patients present with limited disease. Limited disease is confined to one hemithorax and ipsilateral supraclavicular nodes, ipsilateral and contralateral supraclavicular nodes alone, mediastinal nodes alone, or pleural effusion alone. All others have extensive disease (59). The median survival in untreated cases is 14 weeks for limited disease and 7 weeks for extensive disease (9,10).

In limited disease, surgery has a small beneficial effect on survival and radiotherapy a significantly better effect (39). However, patients almost always relapse. Radiotherapy has no effect on survival in extensive disease (40). A possible exception to these observations occurs in the occasional resected solitary pulmonary nodule which turns out to be small cell, with 4/11 five year survivors in one series (41). In two recent reviews surgery followed by chemotherapy is suggested for a select group of patients. A minority of patients with Stage I or II small cell carcinoma (10% of patients at presentation) may benefit from resection followed by multiagent chemotherapy. Five year survivals of up to 25% have been reported in such cases (59,60). These patients were all carefully staged with multiorgan scans, bone marrow biopsies and mediastinal exploration.

Cyclophosphamide compared to placebo in extensive disease shows significant increase in median survival (42). When cyclophosphamide plus radiotherapy was compared to radiotherapy alone, again the chemotherapy group did significantly better (54). Clearly chemotherapy is the treatment of choice for small cell carcinoma (54).

Multiple drug chemotherapy regimens have proven themselves to be the mainstay of treatment (9,10). These have usually been combined with radiation to the primary tumor and mediastinum. Although the necessity of such radiation has been questioned (9), in a recent review thoracic radiation improved local recurrence rates and two year survival in patients with limited disease who received standard chemotherapy. Mean survival time was unchanged, but two year survival was 21% in the chemotherapy and radiation group as opposed to 0% in the chemotherapy alone group. Local recurrence occurred in 80% of patients treated with chemotherapy alone and was reduced to 25% with the addition of radiation therapy (62).

Radiotherapy has taken on another role in small cell cancer therapy. At presentation, approximately 85% of patients have no demonstrable cerebral metastases, yet many of these will develop intra-cranial metastases during treatment (5,9,10). Since most chemotherapy agents do not cross the blood-brain barrier, and micrometastases may already exist at the time of diagnosis, "prophylactic" cranial irradiation (PCI) has been used early in the treatment program. In several studies, this regimen has significantly reduced the subsequent development of CNS disease (44,45). In addition at least one study has shown improved survival in patients with a complete remission who receive PCI (61).

A large scale Southwest Oncology Group study used triple drug chemotherapy (doxorubicin, vincristine and cyclophosphamide), and XRT to the primary site plus PCI (45).

358 patients were treated, 108 with limited disease, 250 with extensive. The results in limited disease: 41% had a complete remission (CR), 75% had CR or partial response (PR). Median survival = 52 weeks. In extensive disease: 14% CR, 57% CR+PR. Median survival = 26 weeks.

On the basis of this and other studies, 15-25% of limited disease patients can be expected to achieve a disease-free 2 year survival. However, only 1-2% of extensive disease patients fare this well. It is hoped that many of these are truly cured (9).

PROGNOSIS AND NATURAL HISTORY OF BRONCHOGENIC CARCINOMA

The figure of an 8-10% five-year survival in patients with lung cancer is widely quoted. However, some large studies are even less optimistic.

In a prospective study of a defined population in Finland, 446 patients developed lung cancer and 19 (4%) survived 5 years (7). These authors cite other larger studies showing 5 to 7% five-year survivals.

The most important prognostic factor for cure is the stage of disease, since cures occur almost exclusively in patients whose tumor can be resected (4).

Among patients with unresectable disease, median survival is determined by (46):

1. Performance status (Karnofsky scale) - Median survival varies directly with performance status, collectively and for each cell type. Weight loss is particularly ominous (47).

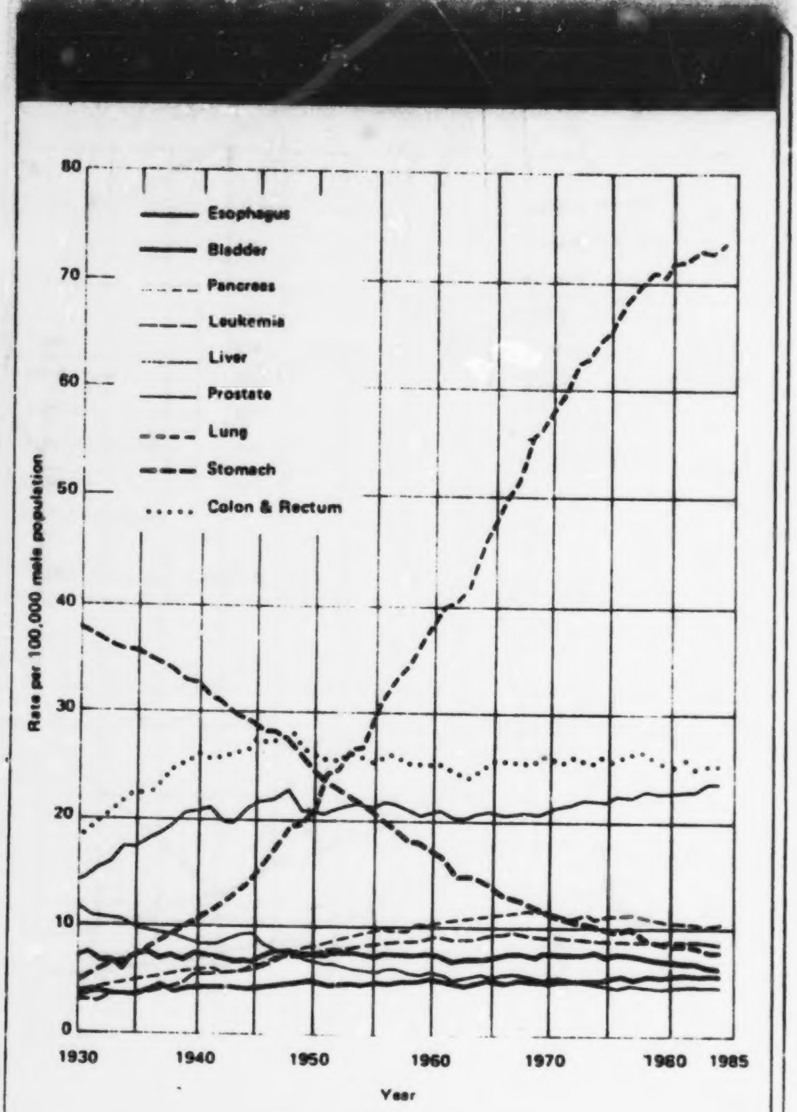
2. Extent of disease - Patients with extensive disease do much worse than patients with limited but unresectable disease.

3. Cell type - Among patients with extensive disease (the majority at presentation), adenocarcinoma (13 weeks average survival) and squamous (19 1/2 weeks) do better than small or large cell (6 3/4 weeks each).

A great deal of effort has gone into programs aimed at "early detection" of lung cancer in high risk populations. The hope is to detect cancer much earlier while it is still resectable, and thus improve these dismal 5-year survival figures. Both annual and semi-annual chest x-rays have been tried. None of these huge mass screening studies has changed the 5-year survival (48). The American Cancer Society no longer recommends any tests for the early detection of lung cancer (48).

The natural history of lung cancer explains the failure of "early detection". If we assume the malignant transformation takes place originally in one cell, and that the tumor then undergoes exponential growth (i.e., constant doubling time), there will be 30 doublings before the tumor is one cm. in diameter, a size just barely detectable on chest x-ray. Average doubling time estimates for cell types are: small cell-29 days, squamous-88 days, adenocarcinoma-161 days. Thus, the time to reach one cm. (30 doublings) is: small cell-2.4 years, squamous-7.2 years, adenocarcinoma-13.2 years (49). If this formulation is accurate, "early detection" is impossible and the cancer will have had adequate time to metastasize before diagnosis if it was biologically predisposed to do so. Figure 3 is an adapted diagram on lung cancer survival (18), and shows outcome in 100 average patients with lung cancer. The key to decreasing lung cancer mortality lies in prevention. To that end encouraging cessation of cigarette smoking is our only real option.

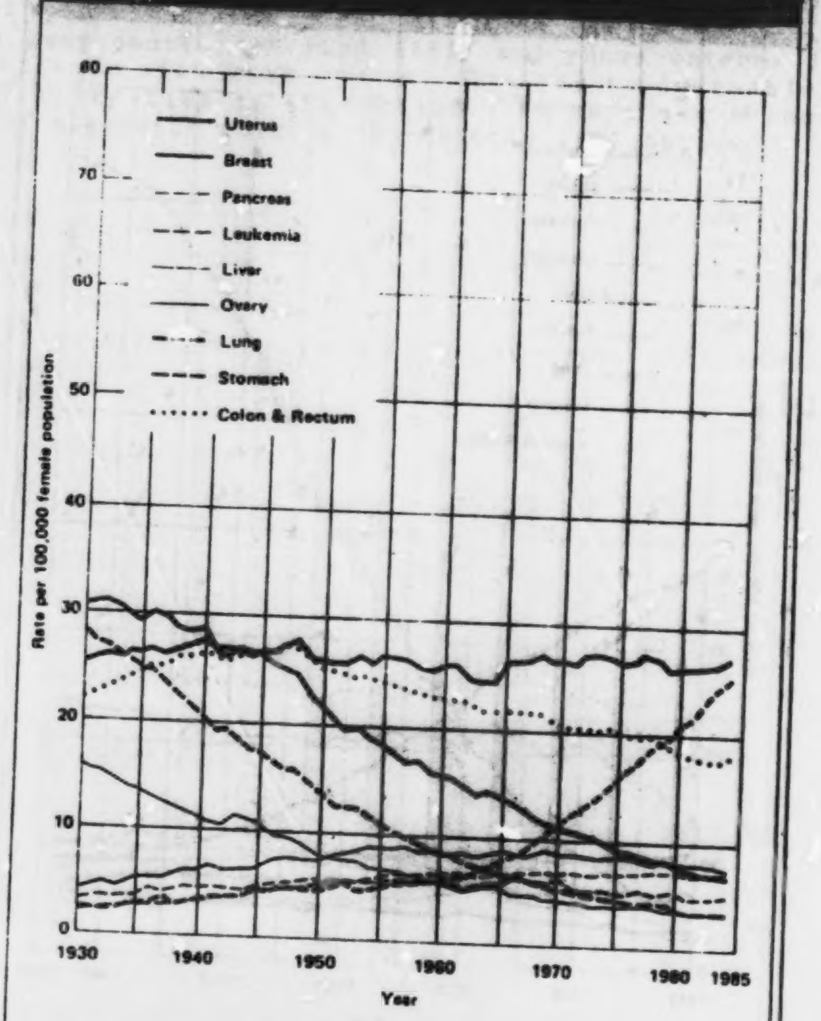
FIGURE 1



Sources of Data: U.S. National Center for Health Statistics and U.S. Bureau of the Census.

*Adjusted to the age distribution of the 1970 U.S. Census Population.

FIGURE 2



Sources of Data: U.S. National Center for Health Statistics and U.S. Bureau of the Census.

*Adjusted to the age distribution of the 1970 U.S. Census Population.

TABLE 1

OCCURRENCE OF FIVE MAJOR TYPES OF LUNG CANCERS IN SMOKERS AND NONSMOKERS

Type	Total	Male		Female	
		Smoker	Never-smoker	Smoker	Never-smoker
Epidermoid	992	892	7	80	13
Small cell	640	533	4	100	3
Adenocarcinoma	750	482	39	128	101
Large cell	476	399	16	46	15
Bronchioloalveolar cell	68	35	4	13	16
TOTAL	2,926	2,341	70	367	148

TABLE 2

SOURCE	MAYO[3]	ARMED FORCES[6]	VA[5]	FINLAND[7]
NUMBER	2.926	3,000	662	431
EPIDERMOID	33.9%	41%	35.2%	45.9%
ADENOCARCINOMA	28.3	28.5	25.2	11.6
SMALL CELL	22.9	25.2	24.6	26.7
LARGE CELL	15.9		14.2	4.9
MISCELLANEOUS		4.9		10.9

TABLE 3

	SQUAMOUS (263 CASES)	ADENO (126)	LARGE CELL (47)	SMALL CELL (114)
Hilar or peri-hilar mass or prominence	40%	17%	32%	78%
Parenchymal Lesion				
Small mass (< 4cm)	9	45	18	21
Large mass (> 4cm)	19	26	41	8
Obstructive pneumonitis. consolidation or collapse	53	25	33	38
Mediastinal mass or widening	1	2	10	13
Pleural effusion	3	5	2	5

TABLE 4

	Hilar or peri-hilar mass or prominence	Small mass (parenchymal	Large mass (parenchymal)	Mediastinal mass or widening	obstruction
Number	246	122	131	30	241
Squamous	42.3%	14.7%	37.4%	6.7%	56.5%
Adeno	8.9	46.7	25.2	10.0	13.0
Large cell	12.6	13.9	30.5	33.3	13.0
Small cell	36.2	14.7	6.9	50.0	17.5

TABLE 5

Initial Symptoms in 2,000 Patients with Lung Cancer

Symptom	Percent of Patients
Cough	74
Weight Loss	63
Dyspnea	58
Chest pain	49
Hemoptysis	29
Lymphadenopathy	23
Bone pain	25
Hepatomegaly	21
Clubbing	20
Intracranial	12
SVC syndrome	4
Hoarseness	18

TABLE 6

Clinical Factors Suggesting Unresectability

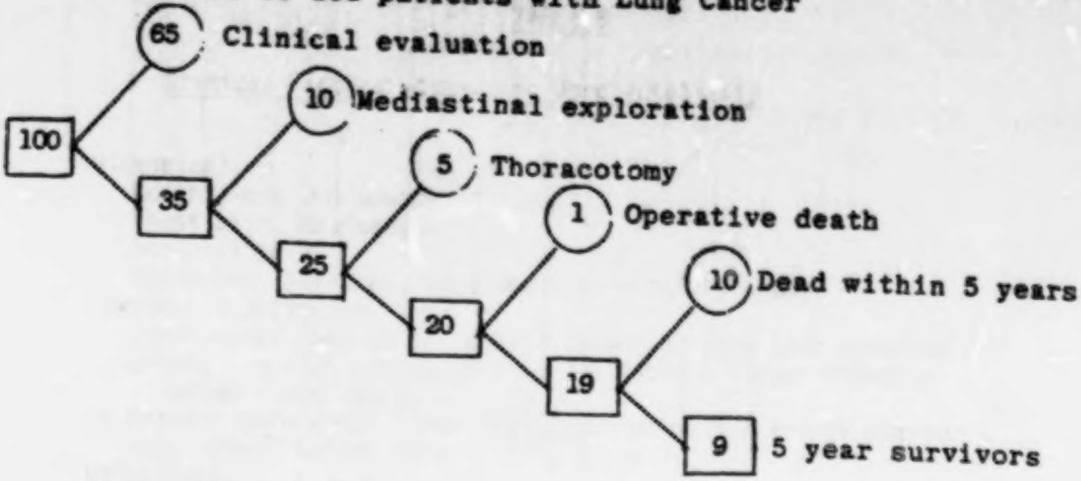
- Historical
  - Weight loss > 8 pounds
  - Chest pain, hoarseness
  - Skeletal pain
  - Headaches, seizures, paralysis, personality change
- Physical examination
  - Lymph nodes (one cm or larger), superior vena cava syndrome
  - Liver, > 13cm percussed span, palpable 3 finger breadths below costal margin
  - Bones: pain and/or tenderness with palpation and/or motion
  - CNS: focal and/or lateralizing signs
- Laboratory
  - Anemia
  - Elevated alk. phos. or SGOT
  - Hypercalcemia

TABLE 7

HORMONE	ASSOCIATED CANCERS
Vasopressin	Oat cell
Corticotropin releasing factor	Oat cell
Corticotropin	Oat cell, carcinoids
Growth hormone	Squamous cell
Prolactin	Oat cell
Melanocyte - stimulating hormone	Oat cell
Parathyroid hormone	Squamous cell
Calcitonin	Oat cell

FIGURE 3

Fate of 100 patients with Lung Cancer


100
65
Clinical evaluation
35
10
Mediastinal exploration
25
5
Thoracotomy
20
1
Operative death
19
10
Dead within 5 years
9
5 year survivors

0 = unresectable (or inoperable)

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MEDIASTINAL EVALUATION IN LUNG CANCER

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Lung cancer is the leading cause of cancer death in men and now the leading cause of cancer death in women in the United States today. With the exception of small cell carcinoma, which is usually considered inoperable at the time of diagnosis, surgical resection of the tumor offers the only hope for long-term survival. Unfortunately only 25% of all patients diagnosed with non-small cell carcinoma of the lung are operative candidates (Figure 1). Of 100 patients diagnosed with bronchogenic carcinoma, 60 will be inoperable because of advanced age, underlying severe medical problems, or poor lung function, or unresectable due to distant metastases. Another 10-15 will appear resectable but on invasive staging will be found to have mediastinal involvement. Of the remaining 25, 5 will be unresectable at thoracotomy, leaving 20 who undergo "curative" resection. (1-4) Once patients who are too old, too sick or have distant metastases are eliminated, careful and accurate staging of the mediastinum becomes the single most important factor in determining resectability and survival.

A working knowledge of the TNM staging system for bronchogenic carcinoma is needed to interpret survival data, and is shown in Figure 2. Occult carcinoma is self-explanatory, referring to positive sputum cytology alone. While the rest of the stages may appear confusing, the system can be considerably simplified if one remembers that Stage II is T2N1M0 - anything lower is Stage I, and anything higher is Stage III (or Stage IV if distant metastases are present, i.e. M1).

The survival data curves in Figures 3 and 4 show that 5 year survival in surgically treated patients markedly decreases as the stage of lung cancer advances from Ia to Ib (i.e. hilar node involvement). The five year survival falls from 53% to 31% respectively. When mediastinal nodes are involved the 5 year survival decreases to 22% in this group of surgical patients (5) (Figure 4). Many authors report even lower 5 year survivals, on the order of 18% with hilar, and 4% with mediastinal nodes involved (6,7). Further expanding this data is a study by Matthews. In an autopsy study of patients dying for unrelated reasons following curative resection for lung cancer, she found a high rate of both locally persistent disease and distant metastases in all cell types of lung cancer (8) (Table 1). Because of this data combined with an overall mortality of 5-10% for thoracotomy with lung resection, many surgeons consider any stage Ib or greater lung cancer, with selected exceptions, to be unresectable. The status of the hilar and mediastinal lymph nodes therefore determines the patient's prognosis and the therapeutic options available.

A thorough knowledge of mediastinal lymph node anatomy is not necessary to understand the patterns of lymphatic spread of lung cancer. Metastases occur first from the primary site to interlobar nodes progressing to ipsilateral hilar nodes, to ipsilateral mediastinal nodes, and then to scalene and cervical nodes. Crossover of metastases from ipsilateral to contralateral mediastinal nodes occurs in up to 30% of cases, and primary lung carcinomas of the left lower lobe have a propensity for metastasizing first to the subcarinal nodes and then ascending via the contralateral mediastinal chain. Peripheral tumors metastasize less frequently to hilar nodes than do central tumors.

Because of its impact on survival and therapy, tissue must always be obtained when assessing the mediastinum in lung cancer. Historically the mediastinum was assessed using standard PA and lateral chest x-ray and mediastinal and hilar tomography. If these films were normal the patient was taken to thoracotomy. Using this method approximately 40-50% of patients were found to be unresectable at the time of thoracotomy. With a mortality of 5-10% and a morbidity of 20% for thoracotomy, alternate staging procedures were sought, and in the late 1950's cervical mediastinal exploration (mediastinoscopy) and anterior mediastinal exploration (Chamberlain procedure) were developed. They remain the gold standard for the pre-thoracotomy evaluation of the mediastinum.

As mentioned, patients with bronchogenic carcinoma and normal chest x-rays and tomography will be found to have positive mediastinal explorations in up to 50% of cases (9,110,11). In an accumulated review of 4983 cases by 28 authors, CME revealed mediastinal metastases in 39% of cases. The resectability rate for patients taken to thoracotomy after a negative cervical mediastinal exploration (CME) increases impressively, as shown in Table 2 (1,3,4,6,12). The resectability rate ranges from 73 to 97% with the average being 89%. CME is clearly a valuable tool in selecting patients who are candidates for surgical resection of bronchogenic carcinoma.

While valuable, CME is limited in its evaluation of subcarinal, anterior mediastinal, and subaortic nodes, which are frequently inaccessible. Patients with left upper lobe carcinomas are particularly difficult to stage via CME. Bowen et al evaluated 28 patients with a negative CME and left upper lobe carcinoma. They performed anterior mediastinal exploration (AME) and found mediastinal node involvement in 30% of these patients (13). Jolly et al confirmed the accuracy of AME in evaluating the mediastinum with left lung lesions. They showed AME and CME to have comparable yields in identifying neoplastic nodes, 38 and 40% respectively. Resectability rates were also comparable for each procedure, 96% with a negative AME and 91% with a negative CME (4). One pitfall in this approach to the mediastinum is that left lower lobe lesions metastasize to subcarinal nodes and then to contralateral mediastinal nodes in virtually all cases. This has led most authors to recommend CME for assessing left lower lobe lesions. Despite these limitations CME and AME are each useful for accurately staging the mediastinum for therapeutic planning and prognosis in bronchogenic carcinoma.

Mediastinoscopy has a morbidity of 1.2% and negligible mortality (14). Reported complications are shown in Table 3. Because of this associated morbidity, and in an effort to reduce the number of invasive procedures and shorten hospital stays, the selective use of mediastinoscopy is advocated. Currently three major non-invasive techniques for evaluating the mediastinum exist: 1) standard radiology (plain chest x-ray and tomography), 2) gallium scanning, and most recently 3) CT scanning . Each of these methods has been extensively studied to discriminate those patients who require mediastinal exploration to rule out neoplastic nodal involvement from those who may proceed directly to thoracotomy.

Several authors have evaluated the utility of standard radiography in predicting mediastinal involvement in bronchogenic carcinoma. Sehlorf et al in a retrospective study found standard radiology to be 88% sensitive and 78% specific in predicting the results of mediastinoscopy, but this study suffered from observer bias. When routine radiographic reports were reviewed the accuracy of standard radiology was only 50% (15). James and Elwood found standard radiology to be 76% sensitive and 95% specific, but they included only clearly positive or negative films in their review and probably overestimated the true utility of standard radiology (16). Kahn et al using oblique hilar tomography predicted mediastinal metastases with a sensitivity of 75% and a specificity of 95% (18). In contrast, Fishman and Bronstein found standard radiology to be only 50% sensitive and 85% specific (17). More recent studies by several authors have found standard radiology to be 12 to 50% sensitive and 90 to 95% specific for predicting mediastinal metastases (28,33,35,37,38).

Whitcomb et al reviewed the ability of standard radiology to predict mediastinal metastases based on the cell type of the primary tumor and location. They confirm an overall low sensitivity for standard radiology of only 50% in unselected cases. Of interest they found that squamous cell carcinoma metastasized to the mediastinum in only 11% of cases, and when the lesion was peripheral the sensitivity of standard radiology increased to 77% in predicting mediastinal metastases. In their study, patients with peripheral primary lesions and normal chest x-rays would have had a 95% resection rate if taken straight to thoracotomy (9).

Overall, standard radiology in unselected patients is too insensitive to select patients for thoracotomy without prior mediastinoscopy. However, in patients with small peripheral primary lesions, negative standard radiology seems adequate to select patients for direct thoracotomy (9).

Many investigators have attempted to use gallium scanning to improve on standard radiology in assessing the mediastinum in bronchogenic carcinoma (Table 4) (19-22). In evaluating the pulmonary hila gallium suffers from a lack of specificity, in evaluating the mediastinum from a lack of sensitivity. When gallium scanning's ability to evaluate the hila and mediastinum are combined, specificity again suffers. For centrally located tumors specificity falls even further secondary to reactive lymphadenopathy. Furthermore nodes less than 1.5cm in size are not detected on gallium scanning, and only 75% of nodes 1.5 to 3.0cm are detected. Finally, adenocarcinoma is not gallium positive in up to 80% of cases. Given all of these pitfalls gallium scanning has little use in assessing the mediastinum in bronchogenic carcinoma.

CT scanning of the mediastinum is being increasingly used as an aid in staging the mediastinum. Many authors have evaluated its role in guiding selective mediastinoscopy and more recently mediastinal needle aspiration (24-38, 42). In comparison to standard radiology most authors have found CT scanning to be superior in assessing the mediastinum for metastases (28,33,35,37,38), but equal to standard radiology in assessing the pulmonary hila (25,31,32,27). Therefore, in guiding selective mediastinal staging CT scanning would be expected to be the superior modality.

The results of all the recently published trials evaluating CT staging of the mediastinum are shown in Table 5. Two older studies using first generation scanners have been excluded (39,40). As can be seen from the table the majority of studies report sensitivities of 80 to 95% with equally high specificities of 70 to 95% and accuracies of 80 to 88% in predicting mediastinal metastases. These authors have recommended that patients with bronchogenic carcinoma and negative mediastinal CT scans should proceed directly to thoracotomy. Using this approach, resection rates of 85 to 90%, comparable to that seen with the routine use of mediastinoscopy, have been achieved (38,41).

Of the studies reporting lower sensitivity and specificity, Mosk and Modini used CT scanners with long scan times and the decreased resolution of these as compared to current scanners may account for their less impressive results. (However, Kahn, using a similar scanner with an 18 second scan time, achieved quite impressive results, so there may be a better explanation.)

More difficult to explain are the results of Libshitz and McKenna. Using a high speed CT scanner and 10mm cuts these investigators found CT to be only 54 to 67% sensitive and 60 to 67% specific with an overall accuracy of 61 to 66% (27,28,33). One explanation is that these investigators performed total nodal sampling at thoracotomy taking both normal and abnormal appearing nodes. Since most other investigators sampled only clinically abnormal nodes, the data of Libshitz and McKenna may more accurately reflect the true sensitivity and specificity of CT scanning in detecting mediastinal metastases. However this is inconsistent with data presented by Rea, who also performed extensive nodal sampling and achieved 80% sensitivity and 76% specificity (34). Alternatively, Libshitz and McKenna do not comment on the distribution of cell types in their series. They may have included patients with small cell carcinoma in which increased micrometastases might be expected. Most other authors excluded patients with small cell carcinoma from their series. Micrometastases in normal sized nodes might account for the decreased sensitivity. Another confounding variable in Libshitz and McKenna's data is a 45% incidence of obstructive pneumonitis, and a 35% incidence of a prior history of granulomatous disease, both of which are well known to produce reactive mediastinal adenopathy and could account for the decreased specificity. The true sensitivity and specificity of CT scanning in detecting mediastinal metastases is probably higher than that reported by Libshitz and McKenna.

Recently, Schenk et al studied transbronchial needle aspiration (TBNA) of the mediastinum in staging bronchogenic carcinoma. The overall sensitivity, specificity and accuracy of TBNA mediastinal staging were 50, 96, and 78%, respectively. No malignant aspirates were obtained in patients with a normal CT scan. Two false positives were due to aspiration of a right paratracheal lung primary in one patient, and contamination of the aspirate by tracheal debris in the other; both were recognized as probable false positives at the time. TBNA is a promising new modality that may obviate the need for surgical staging in selected patients (42).

In summary, CT scanning is a useful test for non-invasively staging the mediastinum. A negative preoperative CT scan results in a curative resection rate at thoracotomy comparable to that achieved with a negative mediastinal exploration. In evaluating the mediastinum CT scanning is clearly superior to standard radiology and gallium scanning. A positive preoperative CT scan, however, does not equate with unresectability. Histopathological staging of the mediastinum by mediastinoscopy or thoracotomy remains the gold standard by which all non-invasive techniques must be evaluated. The role of non-invasive staging is to select those patients that require mediastinal exploration prior to thoracotomy for bronchogenic carcinoma. The following recommendations are made for guiding selective mediastinoscopy in patients with non-small cell carcinoma:

1. A patient with a small peripheral carcinoma and a normal chest x-ray may proceed to thoracotomy.

2. A patient with an abnormal mediastinum by standard radiologic studies requires mediastinal exploration, perhaps preceded by transbronchial needle aspiration, but no further non-invasive studies.

3. All other patients with normal standard radiographs should have a CT scan of the mediastinum (although see recommendation 6 below).

4. Patients with positive CT scans should undergo mediastinal exploration, perhaps preceded by needle aspiration, prior to thoracotomy.

5. Patients with negative CT scans may proceed directly to thoracotomy.

6. We and others (43) recommend CT scanning prior to bronchoscopy to direct the bronchoscopist in performing TBNA at an appropriate site.

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FIGURE 1

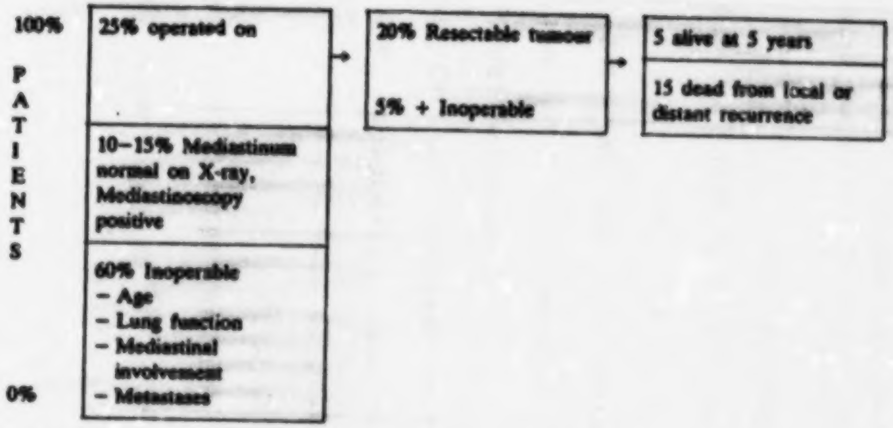

100%
P
A
T
I
E
N
T
S
0%
25% operated on
10–15% Mediastinum normal on X-ray, Mediastinoscopy positive
60% Inoperable
– Age
– Lung function
– Mediastinal involvement
– Metastases
20% Resectable tumour
5% + Inoperable
5 alive at 5 years
15 dead from local or distant recurrence

Fig. 1. The selection of 100 cases of non-small-cell lung cancer for surgery

FIGURE 2

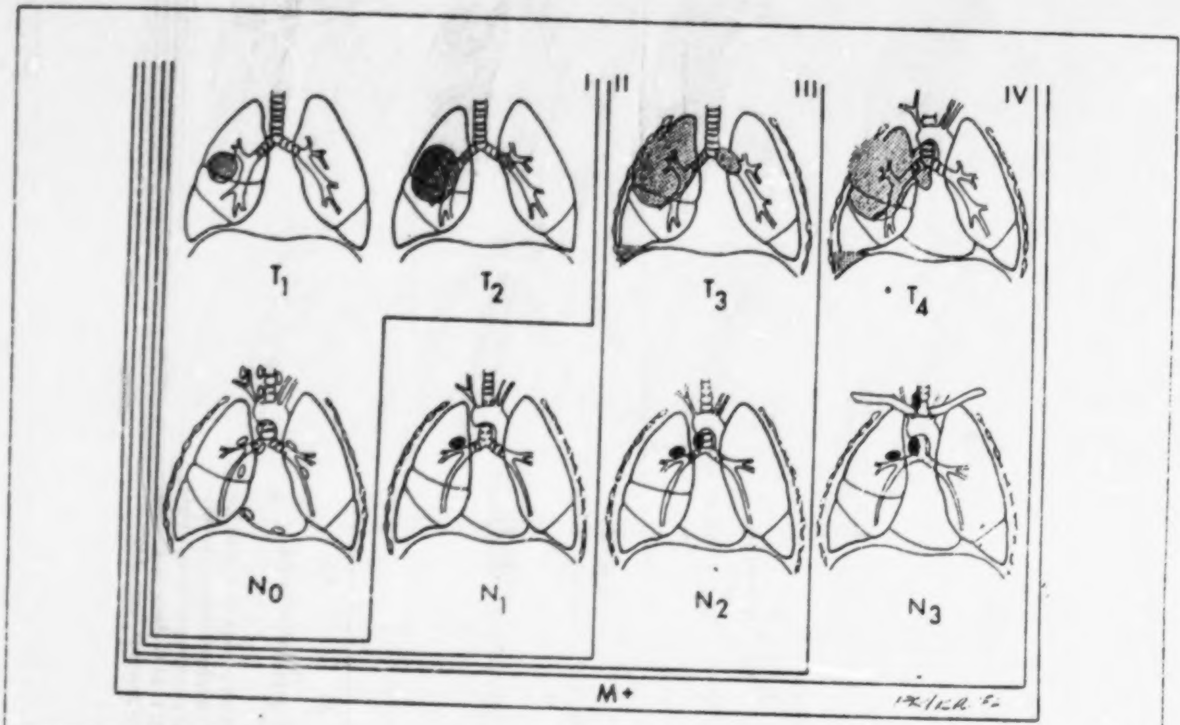


Fig. 13.3 Anatomic staging for lung cancer. *Tumor (T) categories*. *Size* and *confinement to lung* are the major considerations in the progression of non-oat cell cancers: squamous cell carcinoma and adenocarcinoma. T1 vs. T2 depends on the mass being less or more than 3 cm. The depth of invasion is reflected by *extension through the pleura*, which is akin to an organ capsule (T3). Further advancement into mediastinum or chest wall has been designated as T4, although this is not part of the American Joint Committee (AJC) or International Union Against Cancer (UICC) criteria. *Node (N) categories*: Location within the lung *hilar* (N1) or mediastinal (N2) indicates the common progression. Supraclavicular nodes are considered metastatic, although an N3 notation would be reasonable. *Stage grouping* emphasizes the early resectable stages confined to a lobe or lung (T1 and T2) with and without hilar disease (N1) as I and II respectively. Advanced disease (T3), pleural invasion and mediastinal nodes are stage III, with metastases reflecting stage IV. Special TX and N3 categories are not officially used by the AJC/UICC. Tumor (T) and Node (N) equivalents are: T2 = N1, T3 = N2, T4 = N3. *AJC (77) vs. UICC classifications*. T4 is *not* an official designation. Oat cell cancers are usually metastatic or premetastatic and are categorized as intrathoracic or extrathoracic

TABLE 13.1
TUMOR (T), NODE (N) CLASSIFICATION
LUNG CANCER

TX	Positive cytology
T1	≤ 3 cm/no invasion
T2	> 3 cm/extension to hilar region
T3	Gross extension/effusion/atelectasis
N1	Hilar nodes
N2	Mediastinal nodes

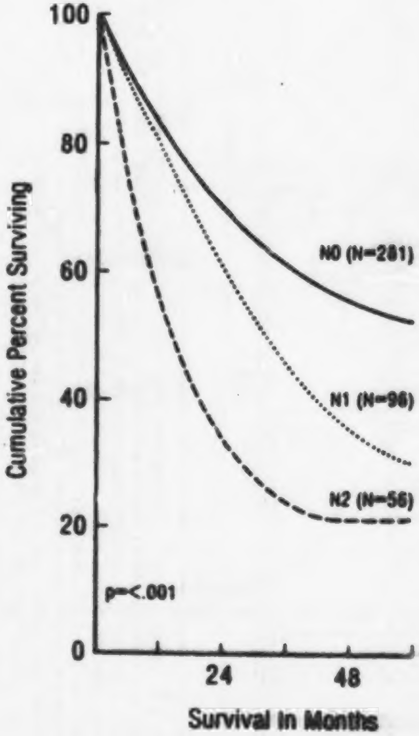
Modified from AJC (77).

TABLE 13.2
STAGE GROUPING
LUNG CANCER

Occult Cancer	TX	N0	M0
Stage Ia	T1	N0	M0
	T2	N0	M0
Stage Ib	T1	N1	M0
Stage II	T2	N1	M0
Stage III	T3	N0, N1	M0
	Any T	N2	M0
Stage IV	Any T	Any N	M1

Modified from AJC (77).

FIGURE 3



Cumulative percentage of patients surviving following apparent complete resection for non-small cell lung cancer: relationship of lymph node metastasis to prognosis (UT, M.D. Anderson Hospital, 1965–1977). Operative deaths are excluded.

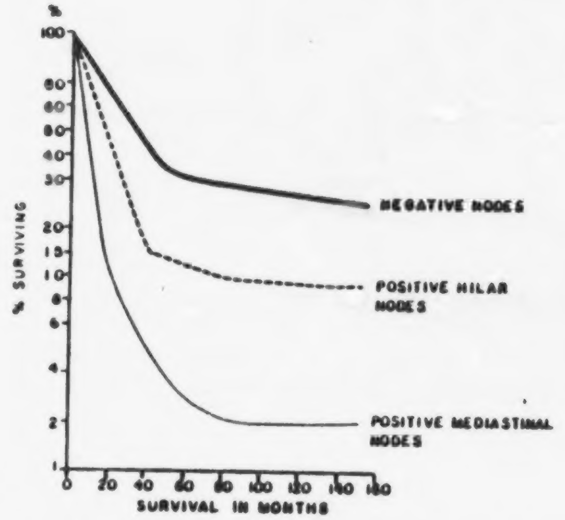


FIGURE 4 Survival as affected by involvement of lymph nodes.[21]

Table 1 Distribution of lung cancer at post-mortem in patients dying within 1 month of "curative" resection (from Mathews et al. 1973)

Type	No.	No. with persistent disease	Distant metastases
Squamous	131	44 (33%)	22 (37%)
Small cell	19	13 (70%)	12 (63%)
Adeno	30	12 (40%)	12 (40%)
Large cell	22	3 (16%)	3 (16%)

TABLE 2

NEGATIVE PRE-OPERATIVE CME

STUDY	PERCENT RESECTABLE
DELARUE 1970	97%
JEPSON 1970	83%
PEARSON 1972	96%
JOLLY 1980	96%
ASHRAF 1980	73%
AVERAGE OF ALL STUDIES	89%

TABLE 3

MEDIASTINOSCOPY COMPLICATIONS

- BLEEDING
    - LOCAL WOUND
    - INTRATHORACIC
- PNEUMONIA
- VOCAL CORD INJURY
- ESOPHAGEAL PERFORATION
- INFECTION
- MI
- TUMOR SEEDING
- AIR EMBOLISM

TABLE 4

GALLIUM SCANNING

STUDY	HILUM		MEDIASTINUM		OVERALL	
	SENS	SPEC	SENS	SPEC	SENS	SPEC
DEMEESTER 1976	100	50	75	83		
WAXMAN 1984	90	62	56	100		
ALZARAKI 1978					100	71
LITTLE 1983					96	59

TABLE 5

STUDY	PTS	SCAN TIME	SENS %	SPEC %	ACCURACY %	ABNL NODE
REA 1981	22	2 SEC	80	76	77	ANY SEEN
FALING 1981	49	2 SEC	88	94	92	>1.5 CM
RICHEY 1984	48	4.7 SEC	95	68	79	>1 CM
DALY 1984	146	2 SEC	80	91	88	>1.5 CM
BREYER 1984	56	2 SEC	82	100	93	>1.5 CM
CONTE 1985	75	5.6 SEC	85	89	88	>1 CM
KAHN 1985	50	18 SEC	83	90	88	>1 CM
SCHENK 1986	88	2 SEC	94	79	85	>1 CM

TABLE 5 (contd.)

STUDY	PTS	SCAN TIME	SENS %	SPEC %	ACCURACY %	ABNL NODE
MOAK 1982	59	NS	50	94	60	>1 CM
MODINI 1982	47	18 SECS	50	97	82	>1.5 CM
LIBSHITZ 1984	86	NS	67	66	66	>1 CM
LIBSHITZ 1984	50	NS	54	67		>1 CM
MCKENNA 1985	102	NS	60	60	61	>1 CM

25. J Thorac Cardiovasc Surg 84: 569, 1982

26. Radiol 156: 552, 1985

27. Am J. Roentgenol 143: 715, 1984

28. Radiol 151: 295, 1984

29. Radiol 156: 295, 1985

30. Chest 88: 206, 1985

31. J Thorac Cardiovasc Surg 90: 639, 1985

32. Radiol 156: 111, 1985

33. Chest 88: 218, 1984

34. J Thorac Cardiovasc Surg 81: 825, 1981

35. Chest 82: 69, 1982

36. J Thorac Cardiovasc Surg 68: 486-494, 1984

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39. NEJM 300: 777-778, 1979

40. J Computer Assisted Tomography 4: 763-765, 1980

41. Radiol 145: 727-732, 1982

42. Am Rev Resp Dis 134: 146-148, 1986

43. Chest 84: 5, 571-576, 1983

COMMUNITY ACQUIRED PNEUMONIA

Charles A. Weber, Captain, USAF, MC

Pneumonia represents the most common cause of death due to infectious disease in the United States (19) and a leading cause of mortality overall. In addition, 3 of 10 Americans get pneumonia yearly with over 500,000 requiring hospitalization. Despite the frequency of acute pneumonias and the wealth of research and literature available on the subject, the exact etiologic diagnosis of acute lower respiratory tract infection in the individual patient often remains elusive. Even when aggressive diagnostic measures are pursued, the exact etiology of a pneumonic process may go undiagnosed greater than 50% of the time (38). This lack of a definitive diagnostic method requires the clinician to take a "best guess" as to the causative organism involved based on careful consideration of epidemiologic patterns and clinical clues. This approach generally allows for adequate therapeutic planning (often empiric), particularly in otherwise healthy adults. To be successful, this scheme requires a systematic approach to the patient as well as a good fund of knowledge of the various pneumonic agents and syndromes. It is the goal of this review to focus on these issues.

EPIDEMIOLOGY

Assessment of several epidemiologic factors will aid in the diagnostic evaluation of community-acquired pneumonia. The most important variables are the age of the patient, the season, the presence of any deficiencies in the natural host defenses against pneumonia, and the environment in which the infection developed.

AGE

The epidemiology of community-acquired pneumonia (CAP) varies markedly with age. This is not to say that a given organism may be completely eliminated from consideration based solely on age, but it will significantly impact on the likelihood that that agent needs to be covered by empiric therapy. An example of this is the increased incidence of childhood pneumonia due to *S. aureus*, an uncommon cause of community acquired pneumonia in the adult. Pneumococcal pneumonia is the most common documentable cause of pneumonia in adults. However, the high frequency of mycoplasma in young individuals (ages 5 to 30 years) as well as the emergence of a previously undefined pathogen in the college age patient (TWAR agent - a strain of *Chlamydia psittaci*) (1) is noteworthy; in certain settings these agents may comprise a majority of the community acquired pneumonias in young adults. The elderly also require close scrutiny due to the increased incidence of gram negative bacillary pneumonia compared to younger individuals.

SEASON

Acute viral respiratory tract infections occur twice as often in winter. An important example of this is influenza pneumonia which occurs characteristically during outbreaks in deep winter. This is important not only for the prevention of primary viral pneumonia but also because of the occurrence of secondary bacterial respiratory tract infection which has a different epidemiology from the usual community acquired pneumonia (there is a much higher rate of pneumonia due to *S. aureus*). Mycoplasma tends to occur year round. Legionella has a tendency to occur in late summer which may be related to distribution of the organism from air conditioner cooling towers in the hot summer months.

HOST DEFENSES

Bacterial pneumonia is unusual in otherwise healthy young adults unless some mitigating circumstance is present such as exposure to a virulent organism or a change in host defenses (2). Although pneumonia may be contracted via the inhalational route (e.g. mycoplasma, legionella, tuberculosis), the great majority of bacterial pneumonias occur as the result of clinically inapparent aspiration of pharyngeal contents. Thus, the increased oropharyngeal colonization by gram negative bacilli in the setting of diabetes mellitus, alcoholism, acute systemic medical illness, prior use of broad-spectrum antibiotics and in the elderly provides a clue that antibiotic coverage should include broad gram negative coverage. Also, conditions or events that might lead to aspiration (alcohol or narcotic usage, protracted vomiting, strokes or dental manipulation) raise the spectrum of anaerobic or mixed aerobic-anaerobic pulmonary disease. Diabetics also have an increased rate of pneumonia due to *S. aureus* compared to the healthy adult (diabetics accounted for one-third of community acquired pneumonias due to *S. aureus* in one study), as well as a higher rate of bacteremia.

ENVIRONMENT

The importance of environmental factors is apparent in two settings. One is that of communicable respiratory diseases such as mycoplasma, influenza and adenovirus which are likely to cause outbreaks of respiratory illness in populations in close quarters such as military recruits, college students and family members. The second factor is an environmental source for a causative organism. The best example of this is legionella which exists in a variety of water reservoirs and can cause epidemics due to a single environmental source.

TYPICAL (BACTERIAL) COMMUNITY ACQUIRED PNEUMONIAS

For purposes of formulation of a diagnostic and therapeutic plan it is helpful to characterize an individual patient's illness as that of a typical bacterial-like illness (abrupt onset of symptoms often associated with rigors, productive/purulent sputum, pleuritic pain, high fever, leukocytosis and tendency for lobar infiltration on chest x-ray) or that of an atypical presentation (to be discussed below). The organisms responsible for typical bacterial community acquired pneumonias include:

1. *Streptococcus pneumoniae*
2. Gram negative organisms
    - *Hemophilus influenzae*
    - Enteric organisms (*E. coli*, enterobacter)
    - *Klebsiella pneumoniae* (another enteric, but frequently presenting in a unique fashion)
3. *Staphylococcus aureus*
4. Anaerobic infections

1. *STREPTOCOCCUS PNEUMONIAE*

General

Pneumococcal pneumonia accounted for greater than 95% of community acquired pneumonias in the pre-antibiotic era (3) and remains the most common documentable etiology for community acquired pneumonia, accounting for between 9 and 76% of these pneumonias in various recent studies. (The wide variation depends primarily on diagnostic criteria employed with less sensitive methods resulting in a low incidence, and less specific methods resulting in a very high incidence.) (7) Of the community acquired pneumonias which require hospitalization, pneumococcal pneumonia accounts for over 70%. Elderly people and asplenic individuals (including sicklers) are at greater risk for this disease. Infection often occurs in the latter part of winter or early spring and commonly follows a nonbacterial (mycoplasma or viral) URI. In the setting of influenza A infection, pneumococcal pneumonia may follow the viral syndrome after a 3-14 day interval, although in one-third of cases the two infectious syndromes will blend together without a gap (4). Eight capsular strains (8,4,5,12,3,1,7,9) account for two-thirds of all pneumococcal infections; type three has a predilection for causing disease in the elderly and is associated with more complications (5).

Clinical manifestations

Pneumococcal pneumonia is the prototype of a bacterial type pneumonia with the typical presentation consisting of abrupt onset of high fever, rigors (80%), rust colored sputum (later turning purulent) (75%) and associated pleuritic chest pain (70%) (6). Leukocytosis typically occurs (15,000 to 20,000) with associated left shift. Marked leukocytosis or leukopenia are adverse prognostic signs (7). The clinical history may be slightly confusing if the bacterial process was preceded by a viral syndrome, thus giving the impression of prodromal illness and therefore an "atypical" picture. Physical findings generally reveal a somewhat toxic appearance and chest findings may include findings of consolidation.

Partial lobar consolidation is classically associated with pneumococcal pneumonia but may actually occur in a minority of cases. However when present, a focal lobar or segmental infiltrate is highly suggestive of a bacterial process and is associated with a high rate (approximately 50%) of bacteremia, (6) compared to an overall rate of bacteremia in pneumococcal pneumonia of 15-25% (8). Bacteremia is associated with a significantly higher mortality (32% versus 6% in non-bacteremic illness) (9); the prognosis for bacteremic pneumococcal pneumonia in the elderly does not appear to have changed since the introduction of penicillin (10).

Diagnosis

Sputum gram stain is usually the only diagnostic specimen available for the clinician prior to institution of antibiotics. Numerous studies have documented the poor reliability of expectorated sputum specimens, particularly regarding culture results. In pneumococcal pneumonia the false positive and false negative rates of sputum culture both approach 50% (45% of patients with bacteremic pneumococcal pneumonia will have negative sputum cultures) (11,12). Others have claimed that a well collected sputum sample (with less than 10 epithelial cells/LPF and more than 25 PMN's/LPF) has greater validity; this type of sample with a good gram stain showing gram positive lancet shaped diplococci seems a reasonable piece of evidence upon which to base initial therapy. (Specimens must be evaluated critically - a study at Mayo Clinic found 75% of expectorated sputums to be inadequate when screened cytologically.) (13) The results of sputum culture are of little value, because of a high rate of oropharyngeal colonization by pneumococcus in the general population (up to 50% of healthy adults), and because even when present as a lower respiratory tract pathogen, pneumococcus may be easily overgrown by other colonizing agents (12). Blood cultures, and culture or positive counter immunoelectrophoresis of pneumococcus from alternate specimens (e.g. paraneumonic effusion) are both highly specific but relatively insensitive, and are not available upon initiation of therapy. Transtracheal aspiration is more reliable than expectorated sputum samples in estimating the cause of pneumonia but again false positive cultures are common, especially in patients with COPD who are frequently colonized by potential respiratory pathogens (12). Culture of any airway specimen becomes even more unreliable if prior antibiotics have been administered.

Treatment

Standard therapy is procaine penicillin 600,000 units IM q12 hours or aqueous PCN G 600,000 units IV q12 hours for 5-7 days or 3 days beyond fever resolution. Alternatives for the less toxic patient include oral penicillin VK 500 mg po q6 hours for 10 days or erythromycin 500mg po q6 hours for 10 days. Erythromycin is also an alternative in the beta-lactam sensitive patient, although some prefer the use of clindamycin or vancomycin (14). Higher doses of parenteral PCN are employed only in the moderate to severely ill patient or in the complicated case (i.e. extrapulmonary suppurative processes).

Prevention

The currently available pneumococcal vaccine includes 23 serotypes and should protect against 87% of pneumococcal pneumonias. The efficacy of the polyvalent pneumococcal vaccine (Pneumovax) appears to be established in young healthy adults. This has not been clearly demonstrated in controlled randomized trials in older high-risk adults for whom the vaccine is primarily recommended, but case control studies suggest efficacy in this population (15). Nonetheless, serious pneumococcal infections are well documented following vaccination. It does appear to be cost effective to administer the vaccine to high risk individuals including all patients with chronic cardiopulmonary disease, residents of nursing homes and other chronic care facilities, asplenic individuals (including sickle cell disease), patients with Hodgkins disease, multiple myeloma, cirrhosis, alcoholism, renal failure, any form of immunosuppression, or diabetes, and to all those over age 65. It appears that fewer than 10% of high risk individuals have been vaccinated. This is unfortunate in light of probable efficacy, the safety of administration (16,17) and given that mortality from pneumococcal pneumonia approaches 50% in the elderly.

2. GRAM NEGATIVE COMMUNITY ACQUIRED PNEUMONIA

Community-acquired pneumonia due to aerobic gram negative bacilli is distinctly uncommon in the non-elderly adult population in the absence of some form of systemic illness or immunosuppression. *Hemophilus influenzae*, a gram-negative coccobacillary organism, has long been recognized as a cause of purulent tracheobronchitis and has recently been shown to be a significant cause of community-acquired pneumonia in adults. Although the exact incidence is difficult to assess, it is estimated that up to 10% of community-acquired pneumonias are due to this organism (18), and it is a frequent cause of admission to the hospital. The organisms responsible are usually nontypable *H. influenzae* (i.e. they lack a polysaccharide capsule). Treatment is primarily with ampicillin and can be hampered by a significant prevalence of resistance to this drug. Alternatives to ampicillin include chloramphenicol, a second generation cephalosporin (particularly cefuroxime) and trimethoprim-sulfamethoxazole (19).

Community-acquired pneumonia due to gram negative rods (GNR) are nearly always due to members of the family Enterobacteriaceae (*Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter*). While representing an uncommon cause of community-acquired pneumonia in healthy adults, GNR assume great importance in the etiology of community-acquired pneumonia in elderly patients. Ebright et al examined the cause of community-acquired pneumonia in elderly non-nursing home patients and found *E. coli*, *Klebsiella* and *Enterobacter* to be causative of community-acquired pneumonia in 21% of patients over the age of 65; these infections had a mortality rate of 71% in this age group (6). Other groups with a high rate of GNR pneumonia include diabetics (who have a high rate of oropharyngeal colonization with GNR) and alcoholics.

Chronic alcohol usage impairs host defenses in several ways. Aspiration is common during periods of altered consciousness. There is a high oropharyngeal carriage rate of GNR, and diminished leukocyte migratory capability. Malnutrition and diminished bone marrow reserve are often complicating factors (10). It is not surprising that respiratory tract infections are a common cause of morbidity in this population. In addition to the usual causes of community-acquired pneumonia, pneumonia in the alcoholic is also frequently caused by legionella, anaerobic (aspiration) organisms and GNRs of which *Klebsiella pneumoniae* appears to be the most common.

K. pneumoniae infection in the alcoholic is an often dramatic,and frequently fatal illness characterized by a sudden onset and severe clinical manifestations (90%), with productive cough (90%), chest pain (80%) and rigors (60%) (20). The patient is generally very toxic appearing, is febrile and produces blood-tinged sputum which shows fat cigar-shaped GNR upon gram staining. The organism is usually easily cultured from sputum. Mortality with *K. pneumoniae* ranges from 20 to 54% and appears to correlate with the severity of underlying disease, advanced age, and other risk factors (6,21). The radiographic findings associated with Klebsiella infection are similar to pneumococcal infection, but the organism has a marked tendency to cause massive consolidation and a bulging fissure ("drowned lung"). Additional findings include early abscess and cavity formation as well as frequent occurrence of empyema (22).

Although controlled data is lacking, community-acquired pneumonia due to GNR is usually felt to be adequately treated by a third generation cephalosporin alone (19). In certain situations the addition of an aminoglycoside may be necessary (23), e.g. if a Pseudomonas species weighed prominently in the differential diagnosis.

3. STAPHYLOCOCCUS AUREUS

S. aureus is an uncommon cause of community-acquired pneumonia in adults with recent series suggesting an incidence of 2-6% (24,25). There is an increased occurrence of staphylococcal pneumonia in diabetics, intravenous drug abusers (via hematogenous spread) and following episodes of influenza A infection. The presentation of primary (inhalational) S. aureus pneumonia is quite variable, ranging from subacute to explosive; patients are usually febrile and toxic. The radiographs in this setting are also variable but tend toward a segmental consolidation with a strong tendency toward abscess/cavity formation (25-75%) (6). Unlike pneumococcus or H. influenzae, S. aureus grows well in sputum culture; failure to grow S. aureus from an adequate sputum sample should lead to doubt about the diagnosis. The treatment of choice is a penicillinase-resistant penicillin (nafcillin, oxacillin, or methicillin) given intravenously in relatively high doses (8 to 12 g/day). As a general rule parenteral therapy for staphylococcal pneumonia should be given until the patient is afebrile for 7 days, and should be followed by an oral agent (14). With the exception of staphylococcal pneumonia occurring in an intravenous drug abuser, it is not necessary to empirically cover for possible methicillin resistance. When this is a concern, vancomycin is the drug of choice.

4. ANAEROBIC PNEUMONIA

This subject is covered in detail elsewhere in this manual. Although I have included these under a bacterial-type presentation, in fact they are much more indolent when developed in a community-acquired setting. (Hospital acquired aspiration disease is often complicated by co-infection with GNR or S. aureus and thus tends to have a more acute presentation.) A predisposing condition (e.g. alcoholism, periodontal disease, seizures, etc.) is found in over 90% of cases (26). Therapy usually requires parenteral antibiotics initially until clinical improvement occurs, followed by several weeks of an oral agent. Difference of opinion exists as to the drug of choice, i.e. clindamycin 450 mg q6 hours versus high dose penicillin. A study by Levison et al concluded that clindamycin was superior to penicillin in the management of anaerobic lung abscess (27). Cefoxitin appears to be a reasonably viable alternative which also adds some GNR coverage. Metronidazole has exclusive anaerobic activity, thus missing some of the facultatively anaerobic organisms that are often partially responsible for aspiration pneumonia; available clinical data also shows a clear failure of metronidazole in several cases of anaerobic pulmonary disease (28).

ATYPICAL COMMUNITY ACQUIRED PNEUMONIA

A wide range of organisms are capable of producing a pneumonic illness which differs from the typical bacterial-like syndromes described above. These organisms can present with a viral-like pattern or a mixed picture (i.e. some features of both viral and bacterial illnesses). Typically the syndrome associated with atypical pneumonia includes a prodromal illness followed by an insidious onset of cough and respiratory symptoms, with frequent extrapulmonary symptoms (such as myalgias, rhinorrhea, etc.) which may occasionally obscure the pulmonary symptoms (e.g. diarrhea in mycoplasma or legionella infections). Although not specific, at times the extrapulmonary symptoms provide important diagnostic clues. The more common causes of atypical pneumonia include:

1. Mycoplasma pneumoniae
2. Legionella spp.
3. Viruses
    - Adenovirus
    - Influenza
    - Varicella
    - Measles
4. Chlamydiae
    - Psittacosis
    - TWAR agent

5. **Mycobacterial pneumonia**
6. **Fungal pneumonia**
7. **Q Fever**
8. **Tularemia**

1. MYCOPLASMA PNEUMONIA

This is a particularly important pathogen in the military because of its transmission by droplet nuclei and therefore its propensity to spread throughout closed populations such as in military barracks (29). Family contact provides another mode of spread with attack rates of 70% for children and 20% for adults (30). Community-acquired pneumonia due to mycoplasma occurs year round but is more frequent in late summer or fall. Incubation time is 2 to 3 weeks, and disease is commonest in the 5 to 30 age range (31).

Clinical manifestations

The clinical spectrum of disease due to M. pneumoniae varies from asymptomatic to full-blown ARDS. The typical patient is one who "feels worse than he looks". There is generally insidious onset of cough with minor headache, malaise, low-grade fever and a nonproductive paroxysmal cough; there is often a disparity between the chest x-ray appearance and the patient's condition (31) (i.e. impressive radiographic findings in a relatively well-appearing patient or vice versa), but the typical x-ray is that of patchy unilateral interstitial infiltrates, occasionally with small pleural effusions.

Mycoplasma pneumoniae infection has been associated with a protean array of extrapulmonary manifestations including pericarditis, myocarditis, bullous myringitis, pharyngitis, pancreatitis, Stevens-Johnson syndrome, meningitis, cerebellar ataxia, peripheral neuropathy and hemolytic anemia (32,33).

Diagnosis

The peripheral WBC is normal in two-thirds of patients. Cold agglutinins (antibodies to the I antigen of the red blood cell) appear at one week and peak at four weeks. A four-fold rise in titer or an initial titer of 1:128 or greater is significant, but insensitive. The test cannot be considered specific, either, as cold agglutinins appear frequently (40%) in viral pneumonias (generally at lower titer) as well as other disorders. Complement fixation testing is the method of choice to diagnose mycoplasma pneumonia; a four-fold rise in titer or an initial titer of 1:64 is diagnostic.

Treatment

Therapy consists of either erythromycin or tetracycline. Both drugs appear to be clinically effective, however, the organism can often be grown from secretions for weeks following therapy. There seems to be no clear advantage to either drug as to its effect on mycoplasma infection, however, when pneunococcal or legionella disease are in the differential, erythromycin is the better choice, whereas tetracycline may appear advantageous if psittacosis or Q fever are considerations) (34). There is generally some improvement clinically by 72 hours, however, it is not uncommon for radiographic worsening to occur during this time, and for the patient to remain febrile. Relapse is reasonably frequent and therefore therapy should be continued for 2 to 3 weeks.

2. LEGIONELLA

Pneumonia due to *Legionella* species could justifiably be discussed under the heading of nosocomial pneumonia, or pneumonia in the immunocompromised host as it occupies a prominent place in both of these categories of illness. It is clear that *Legionella pneumophila* (which accounts for over 98% of legionella infections) needs to be considered in the discussion of community-acquired pneumonia. Of the initial 1000 cases of sporadic legionellosis reported by 1981, fewer than one-third had any underlying disease associated with immunosuppression (35). Thus, while there is a propensity for legionella infections to occur in the compromised host, the majority of infections occur in reasonably healthy adults. The "typical" patient affected is the middle-aged male who uses alcohol and tobacco. Any form of chronic illness, debilitation or immunosuppression appears to significantly increase the risk of contracting legionella. Organ transplant patients appear particularly at risk for both contracting disease and succumbing to it (36).

The organism itself is a small gram negative bacillus which exists as a facultative intracellular parasite. Its reservoir appears to be primarily water from which the organism is often cultured during epidemics. Examples include shower heads and air conditioning evaporative cooling towers. A strong association with air conditioning structures is further strengthened by the tendency for outbreaks to occur in the hot summer months (75% of cases are reported from June to October). The mode of transmission is inhalational via aerosolized droplets; no known person to person or animal to person spread has been noted. Thus, legionellosis is not a contagious disease.

The occurrence of disease due to legionella also varies geographically, with some areas and/or institutions reporting endemicity and other areas a very low incidence of disease. In some areas of England legionella causes 15% of community-acquired pneumonia.

Clinical features

The presentation of legionella is considered to be a mixed picture with some features of both viral and bacterial illness. Generally a prodromal illness is seen consisting of malaise, myalgias and headache occurring 2 to 10 days after exposure. This is followed by a rapidly rising fever usually approaching 40 degrees centigrade, occasional rigors, initially nonproductive cough and generalized toxicity. Headache is common (75%) and may be severe; other prominent extrapulmonary findings include confusion (25-50%) and gastrointestinal symptoms, such as nausea, vomiting, and diarrhea (up to 50% of patients). Physical exam is most remarkable for the degree of toxicity, prostration, and obtundation, which is out of proportion to focal findings. Relative bradycardia occurs with some degree of regularity (36). The radiographic findings are nonspecific, with unilateral infiltrates which commonly progress and become bilateral despite appropriate therapy (37).

Diagnosis

One should suspect legionella pneumonia based on the clinical findings. An aggressive attempt should be made to obtain good samples of respiratory secretions which can be appropriately processed with gram stain (although *L. pneumophila* stains poorly if at all, addition of 0.05% carbol fuchsin to 0.25% safranin counter stain may allow detection). The use of immunofluorescent stains (direct) and sputum culture on buffered charcoal yeast extract will also improve the yield. Both the direct fluorescent antibody technique and culture are highly specific for *Legionella pneumophila*. Unfortunately even with these measures the sensitivity remains less than 50%. Alternatively, serologic diagnosis can be established with a four-fold increase in titer to at least 1:128; a titer of 1:256 in a single specimen is usually accepted as presumptive evidence of infection. Other laboratory data suggestive of legionella infection are hypophosphatemia, hyponatremia, elevated liver enzymes and proteinuria/hematuria.

Treatment

In view of the potential difficulties in ascertaining the diagnosis of legionella pneumonia and its significant morbidity and mortality (30-40% in the original outbreak in 1976 when appropriate antibiotics were omitted) (36), early empiric therapy should be pursued. Erythromycin is generally regarded as the therapy of choice (500-1000mg IV q 6 hours until afebrile for 2 days followed by oral therapy for up to 3 weeks). Rifampin 600mg q 12 hours is suggested as an adjunct to erythromycin in moderate to severe cases. Trimethoprim-sulfamethoxazole appears to be as effective as erythromycin in animal studies. Several points are notable during therapy: while improvement may begin shortly after initiating antibiotic therapy, it is often delayed for several days and high spiking fevers may persist for the first week; radiographic deterioration despite appropriate therapy is commonplace and eventual radiographic resolution may take several months (6).

Mortality in the early series was 15-20%. Currently it appears to be less than 5%, although it remains very high in the immunocompromised host (40-50%) (36).

3. VIRAL PNEUMONIA

Influenza

Influenza A is characterized by a high attack rate. Viral particles are disseminated throughout the airways even in uncomplicated influenza, and previously healthy persons show abnormalities of small airway function. Approximately 7% of exposed individuals develop pneumonia, and the majority of these people have some predisposing condition such as pregnancy, chronic cardiopulmonary disease, diabetes or nephrotic syndrome. In severe cases influenza pneumonia produces hemorrhagic alveolitis resulting in dyspnea, tachypnea and hypoxemia. Abnormal interstitial markings may persist for months, and rarely pulmonary fibrosis develops.

Fortunately most cases are mild with nonspecific patchy lower lobe infiltrates. Diagnosis can be established by serologic methods; however, direct isolation of the virus from respiratory secretions is a sensitive method and allows diagnosis early in the course of the illness. The use of nasopharyngeal washings is the method of choice for viral culture. (There is a high degree of correlation between upper airway findings and lower respiratory tract viral infection.) (39). Newer techniques utilizing RIA or ELISA methods for viral antigen detection may provide a quick inexpensive diagnostic tool.

The influenza vaccine is felt to be 60-80% effective in preventing clinical infection and is currently recommended for elderly people, residents of nursing homes or chronic care facilities, chronic cardiac or pulmonary disease patients, patients with metabolic disease, children on chronic aspirin therapy (at risk to develop Reye's syndrome) and workers at risk of propagating nosocomial spread. Chemoprophylaxis with amantadine (200mg/day orally) is effective in preventing clinical illness in 60-90% of exposed individuals. It should be administered at the outset of an epidemic to high risk individuals who have either not been vaccinated, or have been vaccinated within 2 weeks of exposure, or in whom there is concern about poor response to vaccine. Amantadine appears useful in ameliorating clinical illness from influenza A in adults, however, there is no data to document efficacy in either preventing lower respiratory tract complications of influenza A or in decreasing the severity of established influenza A pneumonia. Primary influenza A pneumonia has a mortality rate of 75% in the elderly.

As previously alluded to, post-influenza A bacterial pneumonia is a fairly common occurrence and is heralded clinically by a biphasic illness with the second phase occurring 3 to 14 days after the onset of the viral syndrome. This appears to be more common in patients with any form of chronic heart, lung or renal disease, and in the elderly. The causative organisms are S. pneumoniae, S. aureus and H. influenzae.

Adenovirus

Adenoviral infections are extraordinarily common in military recruits, especially during basic training. Infection rates approach 100%. Adenovirus type 7 appears to be most commonly associated with pneumonia. A live attenuated oral vaccine (serotypes 4,7) is available for use in military recruits and appears to be highly efficacious (39).

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NOSOCOMIAL PNEUMONIA

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Nosocomial pneumonia, defined as pneumonia neither present nor incubating upon admission to the hospital, is the third most common type of hospital acquired infection; only surgical wound and urinary tract infections are more frequent. However nosocomial pneumonia has the greatest impact on hospital cost and is the most lethal of hospital-acquired infections, accounting for 60% of nosocomial infection related deaths (2). This is obviously a problem of enormous magnitude. Moreover, despite much attention directed at preventing nosocomial infections, the rate of hospital-acquired pneumonia has remained constant while the rate of other types of infection has dropped markedly (8). In one review 15% of all hospital deaths were secondary to nosocomial pneumonia (9).

The great majority of hospital-acquired pneumonias occur in severely ill, debilitated hosts, who have significant breaches, both immune and non-immune, in their ability to defend against respiratory tract infections. These defects are clearly different from the well defined defects in humoral and cell-mediated immunity seen in the typical immunocompromised host; this chapter will be limited to discussion of the "non-immunocompromised" host.

EPIDEMIOLOGY

The etiologic organisms involved in nosocomial pneumonia differ significantly from those in community-acquired pneumonia and thus require a separate diagnostic and therapeutic approach. While gram negative bacilli cause a small percentage of community-acquired pneumonias, they are of paramount importance in nosocomial respiratory tract infections, accounting for up to 60% of nosocomial pneumonias (4). Of the gram negative organisms involved, the great majority are of the Enterobacteriaceae and Pseudomonaceae families:

Enterobacteriaceae

- Escherichia coli
- Klebsiella pneumoniae
- Enterobacter spp.
- Proteus/Providencia spp.
- Serratia marcescens

Pseudomonaceae

- Pseudomonas aeruginosa

The gram negative organisms may be acquired by at least three mechanisms: from the patient's own bowel flora (particularly with the enterics); from the hospital environment (often the case with Pseudomonas and Serratia); or by cross contamination from other colonized or infected patients (10). Review of series reporting the etiology of nosocomial pneumonia shows that among the gram negative rods (GNR), the predominant organisms are always Klebsiella species followed by Pseudomonas species; together these two organisms usually constitute half of all the infections due to GNR (11,12). Most of the surveys of nosocomial pneumonia have relied on culture results of expectorated sputum, which has obvious limitations (i.e. contamination with oral flora, which is often colonized with potential pathogens). A study by Bartlett et al (6) prospectively evaluated nosocomial pneumonias in a VA hospital and pursued a specific etiologic diagnosis by transtracheal aspirate, blood culture or culture of empyema fluid. They did not accept expectorated sputum as a specimen, nor did they include patients who had already received antimicrobials. In this study a surprising number of mixed infections occurred, with aerobic and anaerobic organisms frequently cultured from the same patient (54%). Overall, GNR were cultured in 40%; furthermore in the pure cultures (i.e. a single organism recovered) GNR accounted for 38% of isolates with Klebsiella, E. coli, Proteus mirabilis, and Pseudomonas aeruginosa predominating (6).

The other organism of great importance in the setting of hospital acquired pneumonia is Staphylococcus aureus. Whereas this pathogen is an uncommon cause of community-acquired pneumonia except in certain epidemiologic settings (e.g. the diabetic patient, or during influenza A outbreaks), it accounts for 10 to 28% of all nosocomial pneumonias (6,11,12). The importance of S. aureus in infections of the lower respiratory tract is further amplified by its resistance patterns to beta lactam antibiotics, which vary between hospitals.

The role of aspiration of oropharyngeal contents is well accepted in the pathogenesis of nosocomial pneumonia. Improved specimen collection and bacteriologic techniques have resulted in anaerobic bacteria being recognized as important nosocomial pathogens. The exact incidence of anaerobic hospital-acquired infection is uncertain. The work of Lorber (13) and Bartlett (6,14) suggest pure anaerobic infections cause 4-17% of nosocomial pneumonias, whereas they are co-cultured (? co-pathogens) in 35 to 47%. The contribution of those anaerobic organisms to the pathogenesis of aerobic infections is unclear.

While accounting for a majority of community-acquired pneumonias, S. pneumoniae has been considered to be a relatively uncommon etiology of pneumonia in the nosocomial setting, with incidence reported to be 2 to 10% (11,12). In the prospective study by Bartlett described above, however, pneumococcus was recovered from 31% of patients and represented 30% of the "pure" culture results (i.e. a single organism isolated) (6).

Within the last decade legionella has emerged as a nosocomial pathogen. It appears that the incidence of legionella infection varies widely on a geographic level and also between institutions. In certain hospitals (e.g. University of Pittsburgh, and Wadsworth Veterans Administration Hospital, Los Angeles, California) legionella species caused between 11 and 29% of nosocomial pneumonias. These figures represent "outbreaks" of legionellosis, however. In the absence of such outbreaks, sporadic legionella pneumonia does not appear to be a common nosocomial pathogen except in the immunosuppressed patient, especially the transplant recipient (15,16,22).

Based on the above discussion a reasonable estimation of the bacterial etiologies of nosocomial pneumonias may be as follows:

Aerobic gram negative bacilli	40-60%
Pure anaerobic infections	5-15%
Anaerobic co-infection (?)	20-40%
Staphylococcus	10-30%
Pneumococcus	2-30%
Legionella (sporadic)	<5%

Multiple risk factors have been noted for nosocomial pneumonia, including advanced age, male sex, obesity, tracheal intubation, hospitalization in an ICU, use of antibiotics, upper abdominal and thoracic surgery, severe underlying illness, and mechanical ventilation (1,2). Unfortunately, these risk factors do not appear to be controllable for the most part.

PATHOGENESIS

Two mechanisms appear to be involved most commonly in the pathogenesis of nosocomial pneumonia: aspiration of oropharyngeal contents and inhalation of bacteria-laden aerosols (4). Of these two, aspiration (preceded by a profound change in the oropharyngeal microbial flora) is felt to be of greatest importance.

Normally the oropharynx is colonized by a variety of gram positive anaerobic and microaerophilic organisms, while colonization by gram negative bacteria in normal individuals is uncommon (about 21%). Furthermore in normal persons it is difficult to induce colonization by GNR, despite heavy challenge with large numbers of piliated gram negative bacilli (18). This situation is reversed in the severely ill or chronically debilitated patient. Multiple risk factors exist for colonization of the oropharynx with gram negative rods, but in general the incidence is proportional to the severity of the underlying illness. Patients admitted to a medical ward are 50 to 60% colonized with GNR and patients tracheally intubated and in an ICU rapidly become 100% colonized with GNR (10,17).

The association of colonization of the oropharynx by GNR and subsequent gram-negative bacillary pneumonia appears firm (17). Colonization appears to occur via increased bacterial adherence to the buccal mucosal cells in the debilitated or severely ill patient. It appears that the pili of gram negative organisms may adhere to surface receptors of mucosal epithelial cells. In the normal state these receptors are covered by secretory glycoproteins which prevent bacterial adherence. Fibronectin is one of these glycoproteins, and is cleaved from the epithelial cell surfaces as a result of the excessive proteolytic activity seen in the saliva of severely ill patients. The loss of fibronectin coating from the cell surface allows gram negative rods to bind to the receptors, resulting in increased colonization in vivo (1,19). The oropharynx thus becomes colonized with potential pathogens; movement of even a small inoculum into the lower respiratory tract could conceivably overwhelm the host defenses and cause pneumonia.

Aspiration of oropharyngeal contents is a normal phenomenon during sleep, and generally poses no problem in normal individuals. However, aspiration of even a small quantity of secretions containing GNR may be pathogenic in the seriously ill patient, who often has several factors which contribute to aspiration (e.g. narcotics, obtundation/altered consciousness, impaired gag or cough reflexes, etc.)

Another mechanism involved in the pathogenesis of nosocomial pneumonia is that of inhalation of bacteria-laden aerosolized particles. Overall, this probably plays a much less significant role than aspiration. However this does appear to be the predominant mode of spread for legionella species, which may contaminate hospital water supplies and cause nosocomial outbreaks; another hazard includes contamination of respiratory therapy equipment (e.g. ventilator nebulizers) (20,21) by legionella organisms. Other gram-negative organisms (particularly Pseudomonas and Serratia) occasionally contaminate respiratory therapy equipment and may cause pneumonia by this mechanism (10). This mode of transmission is now rare because of strict infection control measures requiring frequent tubing changes and the use of disposable equipment (1,26).

DIAGNOSTIC APPROACH

Patients with nosocomial pneumonia generally present with a new or progressive infiltrate, fever, leukocytosis, and purulent tracheobronchial secretions. The clinical pneumonic process should begin no sooner than 48 hours after hospital admission. In the evaluation of a pulmonary infiltrate in the hospitalized patient, non-infectious causes such as pulmonary embolus, pulmonary edema, pulmonary hemorrhage, aspiration of gastric contents, etc., must not be overlooked.

After the diagnosis of pneumonia appears secure, the next step is to rapidly assess the likely causes for the infectious process and embark upon a diagnostic and therapeutic plan. One can in general approach the problem from a bacteriologic standpoint since a bacterial etiology is by far the most likely (particularly in the non-immunocompromised host) and because the non-bacterial causes of pneumonia are usually less immediately life-threatening. Unlike community acquired pneumonia in which therapeutic plans can often be based on the clinical setting, the wide variety of underlying illnesses in the hospitalized patient often make this approach unrewarding. For example, a patient may have a fever, leukocytosis and an abnormal chest x-ray due to a co-morbid illness. This, along with the difficulty in obtaining adequate lower respiratory tract secretions for examination, makes the approach to nosocomial pneumonia very difficult. Prior administration of antibiotics may further invalidate the laboratory findings.

The diagnostic techniques usually available to the clinician include examination and culture of material obtained by expectoration, transtracheal aspiration, endotracheal suction, fiberoptic bronchoscopy with protected specimen brushing, transthoracic needle aspiration, or open lung biopsy. For typical bacteria, gram stain will give results within minutes, while the culture results will not be available until after therapy has been initiated. Likewise, blood culture and pleural fluid culture, although specific for the etiologic organism (in the absence of other sources of infection), will require 24-48 hours for results. Open lung biopsy is not generally a consideration in the non-immunocompromised host.

Gram stain and culture of expectorated sputum are the traditional procedures to evaluate the cause of pneumonia. Because of problems with contamination by oropharyngeal flora, culture of expectorated sputum offers little if any diagnostic utility. This has been substantiated in many studies (6, 23-24). An exception to this may occur with S. aureus and gram negative rods; while positive cultures for these organisms may represent false positives, the failure to grow these organisms on culture of expectorated sputum generally excludes their presence in the lower airways (25). Although not completely supported in the literature, gram stain of an adequate specimen of expectorated sputum (>10 WBC/LPF, <25 epithelial cells/LPF) may be useful in guiding initial therapy if a predominant organism is observed (25).

Culture of secretions suctioned via the endotracheal tube is frequently employed in patients who develop pneumonia while on a mechanical ventilator or who require ventilatory support as a result of their pneumonia. There is little to support this approach in the literature, and the bacteriologic results of culture appear to be accurate little more than 50% of the time (27) (i.e. comparable to expectorated sputum).

Transtracheal aspiration has been validated in a number of studies as a method for yielding lower respiratory tract pathogens (25, 28). It is both more sensitive and specific than either expectorated sputum samples or bronchoscopic specimens obtained by suction or by unprotected brushing (3). It is also particularly useful in the diagnosis of anaerobic disease (24) and is the method of choice for obtaining secretions for culture and staining when legionella is suspected (29). Its yield is limited when colonization of the lower respiratory tract occurs, such as in chronic bronchitis, bronchiectasis or recently treated lower respiratory tract infections (3). This procedure should be a consideration if the sputum sample appears to contain multiple organisms on gram stain or if the patient is obtunded and unable to produce sputum (5).

Fiberoptic bronchoscopy has long been used to obtain specimens from the lower respiratory tract for bacteriology. However it is apparent that this instrument provides little advantage over expectorated sputum unless a plugged telescoping catheter device is employed. This technique appears to be a promising method to identify lower respiratory tract pathogens. It does require painstaking technique, as well as a laboratory equipped to do quantitative cultures. Furthermore, the yield of the plugged telescoping catheter is poor if prior antibiotics have been administered. The exact incidence of false positive and false negative culture results with this method is difficult to determine because many of the studies have not adhered to the currently accepted bronchoscopic and microbiologic techniques (25,26).

Transthoracic lung aspiration has also been employed by some with a reported 80% yield and virtually no false positive results (30). Unfortunately pneumothorax occurs in about 25%, with one half of those requiring chest tube placement. Concern for tracking the infection into the pleural space would seem legitimate, but empyema has been exceedingly rare (5).

Several excellent discussions of these procedures and their utility in lung infection are available (25-31,32).

TREATMENT

In the setting of nosocomial pneumonia, empiric therapy is nearly always employed after appropriate microbiologic specimens have been obtained. The choice of therapy should be directed to cover the common pathogens in this setting, namely gram negative rods and *S. aureus*. In the seriously ill patient this will initially include one of the following:

1. An aminoglycoside plus a semisynthetic penicillin
2. An aminoglycoside plus clindamycin
3. Broad spectrum (3rd generation) cephalosporin plus an aminoglycoside (5, 7,33)

Aminoglycoside levels should be measured and therapy adjusted to keep the peak amikacin level $\geq$ 24mg/ml or gentamicin/tobramycin levels $\geq$ 6 mg/ml as this appears to improve outcome in gram negative pneumonia (34).

Other considerations include the possibility of aspiration of oropharyngeal contents with resultant anaerobic pneumonitis (requiring penicillin G or clindamycin in the regimen), and the local incidence of methicillin resistant *S. aureus* which would necessitate the use of vancomycin in initial therapy. Some have speculated on monotherapy using a third generation cephalosporin (such as ceftazidime) in treatment of nosocomial pneumonia (35), but there are insufficient data to make any conclusions.

PREVENTION

Attempts to prevent nosocomial pneumonia have centered around thorough cleaning and frequent changing of respiratory therapy equipment, nebulization of gentamicin and polymyxin solutions, and anti-pseudomonal vaccines. None has been proven beneficial with the possible exception of improved respiratory therapy procedures. Current recommendations include strict handwashing between patients, and identification of high risk patients with subsequent increased efforts to prevent nosocomial infection.

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ASPIRATION AND ANAEROBIC PLEURO-PULMONARY DISEASE

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ASPIRATION SYNDROMES

There has been some confusion in the past over the classification of aspiration pneumonia (1). Recently, Bartlett (2) has provided a classification based on the nature of the inoculum which is aspirated:

1. Toxic fluids ⟶ chemical pneumonitis
   Examples: Gastric acid, hydrocarbons, mineral oil, animal fats.
2. Bacterial pathogens ⟶ bacterial infection.
3. Inert substances ⟶ airway obstruction
   Examples: Inert fluids, particulate matter.

Before discussing these aspiration syndromes, two points need to be understood:

1. Normal healthy individuals aspirate small amounts of material every day, especially while asleep (3). The aspirated material is usually cleared without clinical disease.

2. In most of the "classic" bacterial pneumonias, the pathogen reaches the lungs through micro-aspiration of oropharyngeal contents (4). Inhalation of droplet nuclei is not important in most bacterial pneumonias (such as pneumococcus, Klebsiella, Pseudomonas).

TOXIC FLUIDS: ASPIRATION OF GASTRIC CONTENTS

Aspiration of liquid gastric contents was first described by Mendelson (5). He reported on 40 obstetrical patients who were observed to aspirate gastric contents during anesthesia. Acute respiratory distress occurred and chest x-rays showed infiltrates, but all had stabilized by 2 days and recovered. That clinical picture is considerably more benign than what we see today (6), but aspiration of liquid gastric contents is still referred to as "Mendelson's syndrome".

The pathophysiology of liquid gastric content aspiration has been well studied in experimental animals (2,5). The etiologic agent appears to be hydrochloric acid, rather than enzymes or bile, though a recent report questions this belief (7). Aspiration of fluid with pH <2.5 causes a chemical injury to the lung; higher pH fluids (even pH-neutralized gastric contents) behave as inert substances (see below). The amount of lung injury increases as the pH becomes lower, though there is little additional damage below pH 1.5. Not surprisingly, large volume aspirates that are poorly localized cause the highest mortality rates (6).

In the experimental dog model, the aspirate is seen to spread to the pleura within 18 seconds, and the pH is neutralized within minutes (6). There is rapid damage to the cells of the bronchial epithelium and alveoli, and within hours exudation of fluid protein, PMNs and RBCs is seen in the bronchi and alveoli (6). Physiologically, this results in decreased compliance (stiff lung) and widened A-a DO_2, due to both ventilation-perfusion mismatch and intrapulmonary shunting. The loss of fluid into the lung may be severe enough to cause hypotension. If the animal survives, resolution begins by three days. Bacteria play no part in this experimental acid aspiration syndrome.

The clinical syndrome of gastric content aspiration has been reviewed by Bynum and Pierce (1) in 50 patients with well documented aspiration. All patients had a disturbance of consciousness. Ninety-six percent of patients developed signs within one hour of aspiration in contrast to other articles suggesting a longer "latent period". Most patients had fever, tachypnea, diffuse rales and severe hypoxemia. Approximately one-third had either cough, cyanosis, wheezing or apnea, and one quarter were in shock. Initial chest radiographs showed alveolar infiltrates that involved multiple areas of the lung and were most often (68%) bilateral.

Their subsequent clinical and radiographic course took one of three patterns (1):

1. In 62% the chest x-ray infiltrate did not progress after 36 hours, and resolved within 2-16 days (mean 4.5 days). These patients recovered. Their course resembles the laboratory animals who received smaller quantities of hydrochloric acid or an aspirate of pH > 2.5.

2. Thirteen patients (26%) showed similar rapid improvement but then had clinical deterioration associated with new or extending infiltrates, mostly from 3-5 days after aspiration. Each patient had recrudescence of fever and leukocytosis with at least one potential pathogen recovered from sputum or tracheal aspirate. Eight of these patients died of what is interpreted to be secondary bacterial pneumonia superimposed on chemical injury to the lung.

3. Six patients (12%) had a rapid downhill course to death, with 5 dying within 24 hours. Initial factors significantly more common in this group included: older age,

apnea, shock, and very severe arterial hypoxemia. These patients resemble the laboratory animals who were given larger volumes of hydrochloric acid with a pH of <2.5.

Therapy of gastric content aspiration includes the following:

1. Endotracheal suctioning should be attempted when aspiration is observed (2,6). However, most of the lung damage is almost instantaneous.

2. Bronchoscopy is indicated for any patient who may have aspirated large particulate matter (6). Wolfe and Bone have used fiberbronchoscopy to aid in diagnosis (8). There is little rationale for lavaging the lung with neutral or alkaline solution since the bronchial secretions are buffered within minutes (2,6).

3. As with ARDS of any cause, ventilatory support with intubation, increased F_IO_2 and PEEP is a cornerstone of therapy (2,6,9). There may be an increased incidence of barotrauma post aspiration (10). Prior to intubation, mask oxygen may be used to keep P_aO_2 >60mmHg.

4. Fluid needs may be large initially due to loss of intravascular volume into injured lung; assessment may be difficult due to diffuse rales (2,6,9). Diuresis should be attempted only with adequate monitoring (i.e. Swan-Ganz catheterization) (2,6,9).

5. The use of corticosteroids to reduce lung inflammation/injury is controversial. Bynum (1) found no evidence that steroids helped, and Bone (11) noted an increased incidence of gram negative rod pneumonias in steroid treated patients.

6. Antibiotic use in the immediate post aspiration period is also controversial. However, recent reviews by Bartlett (2), Bynum and Pierce (1), Wynne and Modell (6), and Murray (12), concur in withholding antibiotics until definite evidence of infection is seen. Based on Bynum's (1) series of patients, infection should be considered when a patient more than 2 days post aspiration has advancing infiltrates, new or higher fever and leukocytosis, and increasing purulence of sputum. A reliable culture specimen should be obtained if possible to guide antibiotic selection; if unavailable, coverage should include Enterobacteriaceae, Pseudomonas, S. aureus, pneumococci, and anaerobes.

ANAEROBIC PLEUROPULMONARY DISEASE

Anaerobic pleuropulmonary disease most often arises from aspiration of oral secretions laden with anaerobic bacteria

(2,4,13). In normal individuals, anaerobes outnumber aerobes by 5 or 10 to 1 in saliva; the number of anaerobes is increased further with periodontitis, and this condition is found in approximately 2/3 of patients with anaerobic pleuropulmonary infection (13). As with gastric content aspiration, most patients (>3%) with anaerobic infection have some condition which predisposes to altered consciousness (13); however, 10% of the cases aspirate because of dysphagia (esophageal or neurologic disease). Additional predisposing factors to aspiration include nasogastric intubation, endotracheal intubation and tracheostomy (14).

Patients who develop aspiration-associated lung infection may have anaerobic, aerobic or mixed infection (2,4). The bacteriology of the infection depends on the bacteriology of the oropharyngeal contents which are aspirated. Though normal individuals do have a predominant anaerobic oropharyngeal flora, chronic or acute illness is accompanied by an increase in bacilli in the oropharynx (4). This occurs as a result of illness and may not represent "hospital flora". It is likely that this represents translocation of indigenous fecal flora.

Two important points deserve mention regarding the bacteriology of anaerobic pleuropulmonary disease:

1. Acceptable bacteriologic specimens include transtracheal aspiration, thoracentesis (the two sources in most of the reports discussed), lung puncture, blood culture, and thoracotomy (4,13). Specimens unacceptable include routine or induced sputum, and aspirates through an unprotected catheter or bronchoscope passed through the nasopharynx or oropharynx (4,13). New techniques that have been utilized to diagnose anaerobic lung infections include gas liquid chromatography of specimens of expectorated sputum and fiberoptic bronchoscopy using the protected brush with quantitative cultures.

The chromatographic analysis detects volatile fatty acids that represent metabolic products of anaerobic bacteria. This test may be obviated by simply smelling the expectorated sputum. A putrid discharge probably negates the need for any other microbiologic test. The published experience using the bronchoscope with a protected catheter has been variable. This technique can be considered no better and possibly worse than transtracheal aspiration (TTA) in diagnosing an anaerobic lung infection (20).

The big question in diagnosing suspected anaerobic lung infections by invasive means is not so much which technique should be used as whether any invasive technique should be used at all. If the clinical scenario suggests an anaerobic lung infection in the absence of a pleural effusion many pulmonary consultants will recommend empiric antibiotic therapy.

2. It has been shown that most hospital bacteriology labs have a poor record of culturing anaerobes; hence, we can expect to under-estimate the incidence of anaerobic infection (4). When anaerobes are suspected but cultures turn out negative, it would be prudent to proceed with treatment directed against the anaerobes.

In contrast to the patients Bynum and Pierce (1) described with witnessed gastric aspiration, the actual episode of aspiration of oropharyngeal contents is seldom observed (2). The diagnosis is suspected when typical symptoms (see below) occur in a predisposed host who has roentgenographic changes in a dependent pulmonary segment (2). (The lower lobe basilar segments are dependent when upright; superior segments of lower lobes and posterior segments of upper lobes are dependent when supine.)

There are four well defined syndromes of anaerobic pleuropulmonary infection (Table 1) (13).

TABLE 1: Bartlett's and Finegold's First 143 Cases of Anaerobic Pleuropulmonary Infection by Disease Type (13).

Type of Disease	Number of Cases
Pneumonitis without empyema	44
with empyema	25
Necrotizing pneumonia without empyema	18
with empyema	10
Lung abscess without empyema	30
with empyema	15
Empyema without evidence of parenchymal infection	1

1. Pneumonitis - Presents as a pulmonary infiltrate with no evidence of cavitation (13). It presents as an acute pneumonia with fever; median duration of symptoms prior to presentation ~ 3 days. Leukocytosis is common. It is most likely to occur in basilar segments of lower lobes. Two-thirds of cases are mixed aerobes and anaerobes, probably reflecting the frequency of hospital acquired infection (50%). Treatment should ideally be based on results of transtracheal aspirate. The anaerobic component will respond to IV aqueous Pen G at 2-4 million units per day (15) switching to IM procaine Pen when the patient improves (14). Aerobes present which are not susceptible to PCN require addition of the appropriate antibiotic; in Bartlett and Gorbach's series (14), an aminoglycoside for gram negative bacilli was the most frequent addition. Most patients defervesce in 2-5 days. It is likely that many of these cases of pneumonitis would eventuate in abscess or empyema if untreated.

The other 3 syndromes differ from simple pneumonitis in showing 3 important hallmarks of anaerobic pulmonary disease: putrid discharge (sputum or pleural fluid), tissue necrosis, and indolent course (13).

2. Necrotizing pneumonia - Presents as an infiltrate with multiple small cavities (13). In addition to fever, patients show weight loss, anemia, and marked leukocytosis; there is significant mortality (See Table 2). Thirty-six per cent have concurrent empyema. Although many patients have PCN-resistant *B. fragilis* as part of a polymicrobial anaerobic flora they may respond well to Pen G. Those who are seriously ill should be treated for *B. fragilis* (clindamycin, or penicillin plus metronidazole) until no longer acutely ill or until a reliable culture specimen shows no *B. fragilis* (16). For in-hospital aspiration, empiric coverage should include drugs for gram negative bacilli and *S. aureus* (i.e. clindamycin and gentamicin).

TABLE 2: Comparison of Anaerobic Pleuropulmonary Infections (13).

	Necrotizing Pneumonia	Empyema	Lung Abscess
Concurrent empyema	36%	--	20%
Duration of symptoms prior to presentation (median)	10 days	10 days	12 days
Mean white count	24,200	23,500	14,000
Duration of fever on therapy (median)	5 days	19 days	4 days
Mortality from infection	18%	11%	0
Time for "cure" - clear chest x-ray or small, stable residua (median)	46 days	142 days	56 days

3. Lung Abscess - Presents as a solitary pulmonary cavity measuring at least 2 cm. It may be associated with infiltrate and/or empyema, and strongly favors the posterior segments of upper lobes and superior segments of lower lobes. In Bartlett's series, approximately 1/3 of abscesses developed after admission for pneumonitis. Patients presenting with abscess may have a very long history of symptoms, even 1-2 months (13). The patients have mild leukocytosis, anemia, and fever which is typically less than 102 degrees F (4).

The treatment of anaerobic abscess should include penicillin; clindamycin is not necessary even though *B. fragilis* is recovered in 15-20% (15). High dose penicillin by the parenteral route is best until the patient is afebrile, followed by long term oral penicillin (13). A large scale prospective study comparing intravenous penicillin G (6mU/day) to clindamycin (600mg every eight hours) in the treatment of pulmonary abscess showed a statistically significant difference favoring clindamycin in terms of number of failures of treatment (20 percent versus 0), the mean duration of fever (7.6 days versus 4.4 days) and the duration of fetid sputum (8 versus 4.2 days) (21). Criticism of this study has centered on the relatively low dose of penicillin utilized which may have accounted for the treatment failures. For this reason, many pulmonary consultants tend to recommend high dose penicillin as initial therapy. In the non-penicillin allergic patient, such therapy is less expensive and associated with fewer side effects than clindamycin. In Bartlett and Gorbach's series which is used to support the effectiveness of penicillin, 20% of patients also received an aminoglycoside for mixed anaerobic-aerobic infection as documented by transtracheal aspiration (15). Frequent chest x-rays should be done initially to document drainage of the cavity; if inadequate, some authors advocate fiberoptic bronchoscopy. Bronchoscopy is particularly indicated in edentulous patients and those over 45 because of a high suspicion of carcinoma (4,13). Most patients will defervesce by one week, though cavity closure may take 4-8 weeks.

4. *Empyema* - Presents as an infected pleural exudate (13). Almost all these patients have associated parenchymal pulmonary disease (Table 1), either pneumonia or abscess; a few appear to represent spread of subphrenic abscess (13,16). Fever, weight loss and anemia are typical (See Table 2). The cornerstone of treatment is adequate early drainage via chest tube(s) (17) or open drainage with rib resection (13). The empyema fluid will allow gram stain and culture to guide antibiotic selection more accurately. If the pleural fluid obtained by the diagnostic thoracentesis fails to yield thick pus, institution of tube thoracostomy should be guided by pleural fluid Gram stain and the pleural fluid glucose, pH and LDH levels. If the pleural fluid pH is less than 7.0 or the glucose level is less than 40mg/dl, tube thoracostomy should be performed immediately. In patients with a pleural fluid pH between 7.00 and 7.20 or an LDH level above 1000 u/L serial thoracentesis at 12 to 24 hour intervals may determine the need for a chest tube. If the pleural fluid pH is greater than 7.20, the pleural fluid glucose is greater than 40mg/dl and the pleural fluid LDH is below 1000 u/l, the parapneumonic effusion is in the exudative stage and does not require further diagnostic or therapeutic intervention (22).

ASPIRATION OF INERT SUBSTANCES (2,6)

"Inert substances" have no significant toxic effect on the lung but cause pulmonary problems by mechanical obstruction or reflex mechanisms, with much less inflammation than previously described syndromes.

There are several well-described syndromes involving aspiration of inert solids. Large particulate matter, such as partially chewed meat, may be aspirated by adults and result in obstruction to the glottic opening, the so called "cafe coronary". Smaller food particles, especially vegetable matter (peanut, seed), can be aspirated by small children; if not expelled by coughing, the bolus can lodge in a small bronchus and lead to distal atelectasis and eventually to such syndromes as recurrent pneumonias, bronchiectasis, lung abscess, and lipoid pneumonia.

Inert liquids such as fresh or salt water may cause reflex airway closure or alveolar collapse and atelectasis from surfactant changes, as well as acute suffocation (drowning) if the volume of the aspirate is sufficiently large.

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TUBERCULOSIS

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Tuberculosis is estimated to have been responsible for 30% of all deaths in the 17th century. Despite the decline in tuberculosis-related mortality in the past 20 years (1600 fatal cases reported in 1984), approximately 30,000 new tuberculosis cases are reported each year in the United States (1). Over the past 32 years, there has been a 5-7% decline in the annual morbidity of tuberculosis. If that level of decline holds true in the future, we cannot expect to eliminate tuberculosis until after the year 2100. However, in 1985 tuberculosis morbidity showed little or no decline in this country. The reasons for this static pattern are not known, but the major causes are thought to include:

1. An increasing incidence of infection with the AIDS virus.

2. Tuberculosis outbreaks among the homeless.

3. The influx of immigrants and refugees from areas of the world that have a high prevalence of tuberculosis infection (42).

Therefore, it is likely that tuberculosis will remain a significant health problem in this country for many years to come.

PATHOGENESIS

Tuberculosis is a classic example of a disease controlled almost entirely by cell-mediated immunity, with the macrophage as the effector cell and the lymphocyte as the immunoresponsive cell. Although not fully understood, there are genetic factors which influence the pathogenesis of tuberculosis; for instance, it is known that blacks with HLA BW 15 show a higher incidence of tuberculosis and have a more aggressive disease. However, in the final analysis, what determines whether the disease progresses or regresses is the power of the macrophage to inhibit growth of the engulfed tubercle bacillus.

M. tuberculosis is usually spread by a "droplet nucleus" produced when a person with active tuberculosis talks, sneezes, or coughs. The "droplet nucleus", containing 1-3 bacilli, is inhaled and passes through the mucociliary defenses into the alveoli, usually in the lower lung fields. The larger clumps settle on the surface of the nasal passages and bronchial tree and usually do not cause disease. Once in the alveolus, the bacillus is ingested by the pulmonary alveolar macrophage. If a virulent bacillus is ingested by a macrophage, the bacillus can multiply intracellularly and kill the phagocyte. The bacilli which are released chemotactically attract monocytes (macrophages) from the bloodstream forming a small tubercle. However, before the blood-borne macrophages can be effective they must first be activated. Activation occurs as a result of stimulation by lymphokines which are manufactured and released by lymphocytes (usually T-cells). Cellular hypersensitivity is manifested by a local accumulation of macrophages and lymphocytes caused in part by T-cell chemotactic lymphokines.

Once cellular hypersensitivity has been established, macrophages and lymphocytes rapidly accumulate and may become activated wherever tubercle bacilli and their tuberculin-like antigens exist in tissues. This rapid recognition and reaction (termed accelerated tubercle formation) makes possible the destruction of inhaled tubercle bacilli that were not destroyed by alveolar macrophages, thus preventing exogenous reinfection. Accelerated tubercle formation also stops the progression of small lesions of hematogenous origin in the lung, spleen, liver and kidney, thereby controlling endogenous reinfection. As long as the number of bacilli present in the tissue site is small, cellular hypersensitivity controls disease progression.

If macrophages do not develop enough microbicidal activity, they are killed by bacilli that continue to multiply intracellularly and the disease progresses. The bacilli in pulmonary lesions may drain into the hilar lymph nodes and establish new lesions there. The efferent lymph from these infected nodes may drain into the bloodstream causing secondary foci in the lungs. In addition, bacilli can enter the bloodstream when small blood vessels in pulmonary lesions become eroded by the caseous process. When this occurs secondary foci may develop in the liver, spleen and kidneys. Whether the secondary foci progress or regress depends on the ability of the blood-borne macrophage to limit the growth of the bacilli. In areas of high bacillary antigen concentration, the hypersensitivity reaction can result in cell death and tissue destruction (caseation). This initially beneficial reaction is responsible for almost all of the tissue damage (caseation, liquefaction and tuberculous pneumonia) that occurs in this disease. Liquefaction appears to be due to the hydrolysis of caseous tissue by the hydrolytic enzymes released by macrophages. It is during this process that the tubercle bacilli multiply extracellularly for the first time, often reaching tremendous numbers. When the lesion ruptures into the bronchial tree, the bacilli spread to other parts of the lung and to the environment. The large antigenic load overwhelms the existing immunity. The tuberculous lesions heal when the growth of the bacilli is inhibited by the host defenses. The fibrosis that walls off the caseous focus and closes the cavity is an integral part of the healing process.

MICROBIOLOGY

The tubercle bacillus is an aerobe that thrives at a PO_2 of 100-140mm Hg. Under optimal conditions the bacillus divides only every 16-20 hours (allowing for once daily antituberculous therapy). Resistant mutants occur without exposure to chemotherapy. It is estimated that 1×10^{-6} organisms will be mutants resistant to one drug. This one-drug resistance is independent of resistance to other drugs. The probability that a single mycobacterium, not previously exposed to antituberculous drugs, is resistant to two drugs is approximately 1×10^{-12}. The largest population of organisms in a human infection is approximately 1×10^{9} in cavitary disease. Therefore, the use of two drugs almost always successfully avoids the selection of genetic mutants (2,3), assuming the entire population of organisms does not exhibit resistance to one or both of the drugs, e.g. due to prior therapy.

Mycobacterium tuberculosis exists in three separate populations in tuberculous lesions. As previously noted the largest population (approximately 1×10^{9}) is found extracellularly in cavitary lesions and is actively dividing. A significant number of resistant mutants are found in this large population and therefore a single drug, or an improperly administered dual drug regimen that does not promptly convert the sputum to negative, leads to selective survival of drug resistant mutants and treatment failures. A smaller population ($1 \times 10^{2} - 1 \times 10^{5}$) of bacilli is located in closed caseous lesions where division is intermittent. A third small population lies within macrophages and divides only occasionally. The latter two populations are significant in that therapy must be prolonged if these organisms are to be killed. Bacilli from these closed lesions are frequently the cause of relapse, because of delayed growth of those organisms that had remained dormant throughout therapy, so-called "persisters" (2,3).

RISK OF BECOMING INFECTED

Tuberculosis is very much less infectious than the usual communicable diseases of childhood. It has been estimated that a hospital worker exposed to patients with untreated tuberculosis would have to breathe contaminated air for an average of 600-800 hours to become infected (5). The degree of infectiousness of the source is a pre-eminent factor that determines whether or not a contact will become infected (6-9).

RISK OF DISEASE AFTER INFECTION

Case rates among tuberculin reactors vary markedly with age (10-12). They are high in the early years of life, decrease sharply to a low at 10-12 years of age, subsequently increase to a peak in late adolescence and early adult life, and then again decrease. Female reactors have a slightly higher rate than male reactors during the childbearing ages (12,13). The risk of developing tuberculosis for the newly infected individual (skin test conversion) is approximately 4% per year for the first 1-2 years following infection. For a clinically well person who develops a positive tuberculin reaction from an apparent infection during infancy, the lifetime risk for developing active tuberculosis is probably between 5-10% (14).

SKIN TESTING

There are two predominant techniques of skin testing currently in general use, the Mantoux method and the percutaneous multi-puncture method. Both skin tests are interpreted at 48-72 hours after injection. The Mantoux test is performed by the intracutaneous injection of 0.1 ml of PPD containing 5 Tuberculin Units into either the volar or the dorsal surface of the forearm. The injection should be made just beneath the surface of the skin with the needle bevel upward. Induration diameter is measured and recorded in millimeters. A positive reaction is defined as 10mm or more of induration. The multiple-puncture tests are cheaper and simpler to apply than the Mantoux, especially in large-scale testing programs. Tuberculin is introduced into the skin by either puncture with an applicator having points coated with dry tuberculin or by puncturing through a film of liquid tuberculin. Multi-puncture tests should be used only for screening large populations within a short period of time. A positive multi-puncture test (any degree of induration) should not be considered as diagnostic of tuberculous infection. Verification of a reaction to any multi-puncture test by the standard Mantoux test is recommended unless vesiculation occurs. Immediate reactions to tuberculin tests have no epidemiologic importance and do not indicate tuberculous infection. Severe local reaction should be covered with a dry dressing to prevent secondary infection. Topical steroids have not been shown to be beneficial (15). In most situations, a person whose tuberculin reaction changes from less than 10mm in diameter to 10mm or more in diameter (assuming it increases by at least 6mm) within a period of two years should be considered newly infected (16). If the initial PPD is not significant and a second test given a short time later is positive (i.e. $\geq$10mm induration), the patient is probably displaying the "booster phenomenon" rather than recent infection; this situation occurs frequently in the elderly. A positive tuberculin test usually develops 2-10 weeks after initial infection with M. tuberculosis (4).

Vaccination with BCG usually leads to development of tuberculin sensitivity, although the degree of sensitivity is highly variable. There is no reliable method of distinguishing tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterial infections. Therefore, an IPPD reaction greater than or equal to 10mm in a BCG vaccinated person should be interpreted as indicating infection with *M. tuberculosis* (16).

There are several potential causes for a false-negative tuberculin reaction. Important factors include infection, vaccination with live virus, chronic renal failure, severe protein depletion, malignancies (especially Hodgkin's disease, non-Hodgkin's lymphoma, and chronic lymphocytic leukemia), sarcoidosis, corticosteroid therapy, age (newborns/elderly), overwhelming infection with *M. tuberculosis*, stress, surgery and burns. False-negative results may occur in up to 30% of elderly patients with serious illnesses. Other significant factors include the tuberculin preparation used, method of administration, and interpretation of test results. There are two preparations of tuberculin currently available in the United States, Old Tuberculin (OT) and Purified Protein Derivative (PPD). Old Tuberculin is available only in multi-puncture devices. The standard test dose of commercially prepared PPD is defined as the dose of the product that is biologically equivalent to 5 TU of PPD-S. Commercially labeled 1TU and 250TU products are not bioassayed. They contain respectively one-fifth and fifty times the concentration of antigen determined to be bioequivalent to 5 TU PPD-S (16). A false positive PPD may be secondary to misinterpretation of the skin test results, administration of the wrong dose (i.e. 250 TU) or possibly a nontuberculous mycobacterial infection. The second strength PPD (250TU) should not be used for the diagnostic evaluation of patients suspected of having tuberculosis.

BCG

Bacille Calmette-Guerin (BCG) is an attenuated strain of *Mycobacterium bovis*. The protection afforded by BCG worldwide varies from 0-80% (18). A World Health Organization sponsored trial in India in 1966 involving 250,000 persons found no protective effect of BCG (19). The World Health Organization, however, recommended maintaining the BCG policy in countries with a high risk of infection. BCG vaccine should be administered as early in life as possible (preferably to newborns when feasible or to children less than one year of age) with revaccination in the first year of school. BCG has a protective effect in young children in all studies (20). Thus, the objective of using BCG in control programs is to prevent childhood tuberculosis.

THERAPY

In the past the standard chemotherapy regimen of 18-24 months was easily understood by physicians, since the length of sanatorium treatment had often been in this range. Patients, however, had a history of non-compliance with the prolonged therapy. In the United States, one-fourth of all sanatorium patients left against medical advice (21). Short-course chemotherapy became possible with the development of rifampin. In 1980 the ATS and CDC approved shortening the course of therapy to nine months when rifampin and INH are given together (22). Recently, a 6-month regimen consisting of INH, rifampin and PZA given daily for 2 months followed by INH and rifampin for 4 months was approved by the American Thoracic Society. Ethambutol should be added initially if drug resistance (INH) is suspected (23), although bacteriostatic drugs as a rule have little or no place in short-course chemotherapy. The following table outlines drugs used in short-course chemotherapy (2).

SHORT COURSE CHEMOTHERAPY

DRUG	DOSAGE		ACTIVITY
Bactericidal Drugs	Daily	Twice Weekly	
Streptomycin (SM)	15-25 mg/kg 5d/wk	25-30 mg/kg	Active against extracellular bacilli in cavities.
Capreomycin (CAP)	0.75-1gm 5d/wk	1.5 gm	Same as streptomycin
Isoniazid (INH)	5-10mg/kg usually 300 mg po	15mg/kg usually 900 mg	Active against both extracellular and intracellular bacilli
Rifampin (RIF)	10mg/kg usually 450-600 mg po	10mg/kg usually 450-600 mg po	Same as INH esp. on closed lesions (persisters)
Pyrazinamide (PZA)	30-35mg/kg usually 1.5-2gm	50-60mg/kg usually 1.5-3gm	Intracellular bacilli (acid pH medium)
Bacteriostatic Drug			
Ethambutol (EMB)	15-25 mg/kg usually 1200-1600 mg po	50mg/kg po	Both intracellular and extracellular bacilli, inhibits development of resistant mutants

Streptomycin appears to be the most bactericidal drug for the large, rapidly multiplying extracellular population of tubercle bacilli in cavitary lesions. INH and rifampin are also very effective against this population. Pyrazinamide (PZA) is bactericidal for the intracellular bacilli within the macrophages, as are INH and rifampin (24-26).

The combination of INH and rifampin is bactericidal for all three bacterial populations in a tuberculous lesion. A regimen of INH 300mg and rifampin 600mg daily for one month followed by rifampin 600mg and INH 900mg (15mg/kg) twice weekly for another eight months has been successful in over 96% of patients treated. Daily therapy with INH plus rifampin was no more effective than twice weekly therapy (27,28). Neither streptomycin nor ethambutol adds anything to the effectiveness of INH and rifampin in the absence of INH resistance (29). The CDC recommends examination of the sputum of patients with pulmonary tuberculosis at two-to four-week intervals until conversion occurs. This is to provide objective evidence of the patient's response to therapy and to estimate the level of patient infectivity (45).

Costs are markedly reduced with short-course therapy for two reasons: a smaller amount of drugs is required, especially when administered twice weekly, and a shorter period of time is required to monitor patients during treatment.

INH resistance should be suspected if the patient has received previous chemotherapy, has infection that was probably acquired in a country with a high prevalence of INH resistance (Asia, Latin America, Africa), or has disease acquired through contact with an INH-resistant patient. In a suspected INH resistant patient the combination of INH/RIF/PZA/SM given initially for 6-8 weeks or until the results of susceptibility testing are available will reliably avoid developing resistance to another drug. With this combination, there will be at least two bactericidal drugs active against the bacilli in all three populations even if they are resistant to INH. If INH sensitivity is found, the therapy is changed to INH and rifampin either daily or twice weekly for the remainder of nine months. If INH resistance is demonstrated, SM/RIF/PZA are continued for a total of nine months. They may be given twice weekly with equal efficacy compared to daily therapy (2,30,31).

Bacteriostatic drugs (ethambutol, ethionamide, cycloserine, PAS) may be indicated when the side effects of the bactericidal drugs restrict their use in proper combination for short-course chemotherapy or in the presence of multiple drug resistance when the use of two effective bactericidal drugs is precluded. Reliance on bacteriostatic drugs makes it necessary to lengthen therapy to 18-24 months in order to prevent relapse. Ethambutol can be substituted for rifampin when toxicity precludes its use, providing the duration of therapy is extended to 18 months. This is not possible, however, when toxicity forces the withdrawal of INH. When rifampin and ethambutol have been used in smear positive cases, the relapse rate has been almost 25% (29). Therefore, when INH must be withdrawn in a smear-positive case substitution should be with streptomycin and PZA, not with ethambutol.

Patients on effective chemotherapy lose their infectiousness for others rapidly. Many physicians feel that for an average sputum-positive patient the hazard is minimal after one to two weeks of effective chemotherapy. Initial treatment at home is not absolutely contraindicated in the patient who has been living at home prior to diagnosis (32).

EXTRAPULMONARY TUBERCULOSIS

Despite the decreasing incidence of tuberculosis in the United States, extrapulmonary disease represents an increasing proportion of all cases. New ATS guidelines for the treatment of extrapulmonary tuberculosis include INH/rifampin short course therapy or the 6-month regimen recommended for pulmonary tuberculosis (23). Several patients with various medical problems including diabetes mellitus, prior gastrectomy, various malignancies, etc. have been successfully treated with the short-course regimen (33). Theoretically extrapulmonary tuberculosis should be no more difficult to treat effectively than pulmonary tuberculosis. A large number of extrapulmonary tuberculosis patients have been treated with rifampin and INH, many twice weekly, for a total of 9 months without relapse or failure (34).

CHEMOPROPHYLAXIS

Chemoprophylaxis refers to the prevention of overt clinical disease after tuberculous infection has occurred. In reality such treatment is single drug therapy for subclinical tuberculosis (35). At any age the risk of developing tuberculosis is greatest shortly after infection. Tuberculous infections occurring in infancy and adolescence carry a high risk of rapid development of disease. The younger tuberculin reactor is more likely to have been infected recently and is therefore at higher risk of developing disease. This same patient is at a lower risk for developing INH hepatotoxicity. The ATS and Public Health Service have therefore recommended INH prophylaxis in all infected persons up to age 35. For people older than 35 who react positively to IPPD, "prophylactic" INH is recommended when the following additional risk factors are present: evidence of recent tuberculous infection (skin test conversion within two years), household exposure to an infectious case, an abnormal chest x-ray (specifically a fibronodular infiltrate), diabetes mellitus, immunosuppressive therapy, silicosis, post-gastrectomy, intestinal bypass, peptic ulcer disease, malabsorption syndromes, AIDS, HIV positivity, clinical conditions associated with rapid weight loss or chronic undernutrition and chronic hemodialysis (3,23,35). The risk of developing tuberculosis for infected contacts may exceed 1% the first year after the detection of the index case and may diminish to less than 1/10th of 1% a decade later. However, because of their long life expectancy, the cumulative life time risk for young infected contacts may be as high as 10% (37-39).

Only INH has been demonstrated to be effective prophylactically. The protective effect of INH when used to treat established tuberculosis infection persists for decades beyond the treatment period and probably for life (40). Current recommendations are for INH 300mg daily for 9-12 months.

When there has been unquestioned exposure to INH-resistant organisms, especially in children and other high risk infected persons, treatment with rifampin, either alone or with INH or ethambutol, could be attempted (3,23). However, when the source of infection is in question INH should be given. A third alternative is to observe the patient for several years and treat for tuberculosis with appropriate drugs if clinical disease develops (35). Adverse reactions to INH are uncommon in patients receiving chemoprophylaxis. INH, however, is capable of inducing hepatocellular injury. Ten to twenty percent of patients receiving INH experience some transient increase in hepatic enzymes while taking the drug. These abnormalities tend to resolve even if INH is continued (3,41). Progressive liver damage may occur in 1-2% of persons over the age of 35. Liver injury can occur at any time during treatment and is an absolute indication to stop the drug. The hepatocellular damage is generally reversible, but if isoniazid is continued in the face of symptoms, hepatic damage can be fatal (35). If the transaminase exceeds 3-5 times normal, INH should be discontinued (3). A major risk factor related to INH liver toxicity is alcohol ingestion (especially on a daily basis). Alcohol ingestion should not be considered a contraindication for preventive therapy in high risk individuals but rather as an indication for monthly transaminase evaluation throughout the course of therapy (42).

Routine liver function studies are not recommended to monitor preventive INH treatment for patients under 35 years of age (3), but monthly biochemical monitoring of active duty Air Force personnel is required by regulation. Individuals over the age of 35 should have a transaminase evaluation at the start and periodically during the course of therapy (3). There has never been a death due to INH hepatotoxicity reported in any study in

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which transaminase levels were monitored routinely. In the pregnant patient, INH prophylaxis should be deferred until postpartum unless the patient is newly infected or another urgent indication exists (35). The pregnant patient with tuberculosis, however, must be treated without delay.

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NON-TUBERCULOUS MYCOBACTERIA

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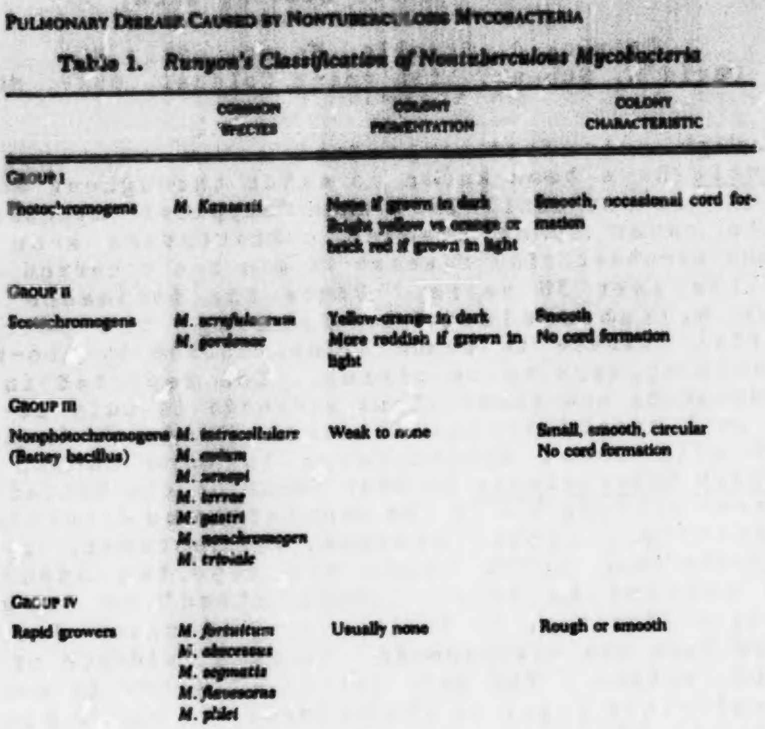
Although acid fast organisms other than Mycobacterium tuberculosis have been known to exist throughout most of this century, it was not until 1954 that "atypical" mycobacteria were thought to cause human disease. Statistics show that non-tuberculous mycobacterial disease in man has occurred at the same rate for the last 30 years. Since the incidence of disease caused by M. tuberculosis is falling, the percentage of mycobacterial disease in human beings caused by non-tuberculous mycobacteria appears to be rising. The reported incidence of disease caused by non-tuberculous bacteria is only 10-15% of all patients with mycobacterial disease. Evidence indicates that infection with these mycobacteria is more common than with Mycobacterium tuberculosis in many areas of the United States and in some cases exceeds 70% of the population as determined by skin test reactivity. Actual disease, by contrast, is uncommon. Between 2,000 and 3,000 cases are reported annually. The infected patient is often "compromised" by lung disease, alcoholism, malignancy, or debilitating illness. Presumably man is infected from the environment. No good evidence of man-to-man transmission exists. The main portal of entry is postulated to be the respiratory tract in the majority of cases although this is not proven. The organisms are found in soil, water, and raw milk and have been isolated from birds, mammals, fish and reptiles. There is an interesting geographic distribution of the non-tuberculous mycobacteria. M. avium-intracellulare disease is more commonly noted in the Southeastern United States, Western Australia and Japan. M. kansasii disease is more frequently found in Texas (Dallas), Chicago, New Orleans, Kansas City, England and Wales. Cleveland, Houston, and St. Louis report approximately equal numbers of pulmonary infections with each species.

CLASSIFICATION

In 1959 Dr. H. Runyon developed a classification scheme based on the niacin test, colonial pigmentation, colonial growth rate, morphology, catalase activity, drug resistance, and pathogenicity for animals. The Group I organisms (photochromogens) form a yellow-orange to brick-red pigment 6-12 hours after exposure to light for one hour. The Group II organisms (scotochromogens) form pigment that is yellow or orange if grown in the dark and more red if grown in the light. The Group III organisms (non-chromogens) are colorless or manifest only a faint yellow-tan color which is not influenced by light. The Group IV organisms are rapid growers with well developed cultures by 7-14 days of growth.



PULMONARY DISEASE CAUSED BY NONTUBERCULOUS MYCOBACTERIA

Table 1. *Runyon's Classification of Nontuberculous Mycobacteria*

	COMMON SPECIES	COLONY PIGMENTATION	COLONY CHARACTERISTIC
GROUP I			
Photochromogens	*M. Kansasii*	None if grown in dark Bright yellow vs orange or brick red if grown in light	Smooth, occasional cord formation
GROUP II			
Scotochromogens	*M. scrofulaceum* *M. gordonae*	Yellow-orange in dark More reddish if grown in light	Smooth No cord formation
GROUP III			
Nonphotochromogens (Battey bacillus)	*M. intracellulare* *M. avium* *M. xenopi* *M. terrae* *M. gastri* *M. nonchromogen* *M. triviale*	Weak to none	Small, smooth, circular No cord formation
GROUP IV			
Rapid growers	*M. fortuitum* *M. abscessus* *M. smegmatis* *M. flavescens* *M. phlei*	Usually none	Rough or smooth

(Medical Clinics of North America 64:433-446, 1980)

Often other non-tuberculous mycobacteria are not easily placed into groups by the differentiating criteria of Runyon. Other methods of classification include agglutination and complement fixation, seroagglutination and immunofluorescent techniques, immunodiffusion, and differential skin testing.

DIAGNOSIS

The diagnosis of non-tuberculous mycobacterial disease is often difficult. Unlike M. tuberculosis, isolating non-tuberculous acid fast organisms from the sputum does not always correlate with infection. Skin testing is not always helpful because many surface antigens are shared among the mycobacterial species. It is not surprising that extensive cross-reactions interfere with proper interpretation for diagnostic purposes. In addition, most of the special skin test antigens available have not been standardized for bioequivalence. Perhaps the most significant finding on skin testing is a negative or small reaction to IPPD in a patient with cavitary disease and sputum positive on smear for acid-fast bacilli (2). A Tuberculin Unit is defined as the activity contained in a specified weight of a standard PPD reference powder and the potency of other batches may be standardized for bioequivalence against this standard PPD by bioassay in humans and animals. There is no such potency standard for the other antigens. Therefore, the results of skin tests are difficult to interpret. Test antigens available in the United States prepared by the CDC include PPD-B (*M. intracellulare*), PPD-G (*M. scrofulaceum*), and PPD-Y (*M. kansasii*) (3). Generally, all non-tuberculous mycobacteria are niacin negative whereas Mycobacterium tuberculosis is niacin positive. The atypical mycobacteria are nonpathogenic for guinea pigs. The isolation of mycobacteria from diseased tissues which are normally sterile indicates a definite cause-and-effect relationship, provided all other more likely pathogens have been excluded. Results of smear and culture of sputum require careful scrutiny even in the presence of compatible pulmonary disease. Guidelines from the National Jewish Hospital and Research Center include: (1) the organisms must be isolated repeatedly from the same source over a period of days or weeks, (2) the organisms must be isolated in significant numbers, (3) a compatible disease process as determined by roentgenogram or other diagnostic procedures must be present, (4) other pathogenic organisms have been excluded and (5) when an underlying disease process is likely, pathologic examination is helpful to establish the role of a possible mycobacterial pathogen. The isolation of Mycobacterium on culture from tissue is strong evidence of disease (3,4).

GENERAL

Non-tuberculous mycobacterial pulmonary disease most commonly resembles tuberculosis. *M. kansasii* and *M. avium-intracellulare* are the most common pulmonary pathogens. Just as with tuberculosis, there is great variability in the historic and clinical presentations. Predisposing conditions include pneumoconioses, previous tuberculosis, chronic bronchitis, COPD, bronchiectasis, and chronic aspiration from esophageal disease. Cases, however, do occur in young patients with no evidence of pre-existing disease. There is a strong association between silicosis and mycobacterial disease. There is, additionally, a strong correlation between malignancy and mycobacterial disease. In one study from M.D. Anderson, the incidence of mycobacterial infection among cancer patients was three times higher than that among the general population of the state of Texas (5).

Roentgenographic features of non-tuberculous infections are reported to differ from those of *M. tuberculosis*. It has been shown that up to one-third of patients with non-tuberculous mycobacterial pulmonary disease will have large upper lobe cavities with well demarcated thin walls, without evidence of bronchogenic spread to the bases or pleural reaction.

The most common etiologic agents causing soft tissue infections are *M. fortuitum - chelonei*, *M. marinum* and *M. ulcerans*. Skin lesions may be manifested by draining sinus tracts associated with underlying lymphadenitis and osteomyelitis, cutaneous dissemination, localized abscesses, or cutaneous granulomas with ulcers. Bone and joint disease may be manifested by deep hand infections, usually secondary to *M. kansasii*, *M. avium-intracellulare*, or *M. marinum* in persons prone to hand trauma. Genitourinary disease manifests as nephritis secondary to *M. kansasii* or *M. avium-intracellulare*, or epididymitis most commonly secondary to *M. xenopi* or *M. kansasii*. Disseminated disease can occur especially in immunosuppressed hosts. Organisms most commonly associated with dissemination include *M. avium-intracellulare* and *M. kansasii*. The mortality rate associated with disseminated disease is usually related to the underlying disease (3).

TABLE II

DISEASE	COMMON SPECIES	OTHERS
Chronic pulmonary disease in adults	*M. avium* complex *M. kansasii*	*M. xenopi* *M. simiae* *M. fortuitum* *M. scrofulaceum* *M. szulgai*
Local lymphadenitis in children	*M. scrofulaceum* *M. avium* complex	*M. kansasii* *M. fortuitum* complex
Skin and soft tissue		
Swimming pool granulomas	*M. marinum*	
Sporotrichoid	*M. marinum*	
Local abscess	*M. fortuitum* complex	
Buruli ulcer	*M. ulcerans*	
Skeletal (Bone, joint, tendon)	*M. kansasii* *M. avium* complex	*M. fortuitum* complex *M. marinum*
Disseminated	*M. avium* complex *M. kansasii*	*M. fortuitum* complex *M. scrofulaceum*

(American Review of Respiratory Disease 119:107-159, 1979)

MYCOBACTERIUM KANSASII

In some areas of the world, this species is the major cause of mycobacterial pulmonary disease other than that attributable to Mycobacterium tuberculosis. It may constitute as much as 20% of all disease caused by mycobacteria in some geographic areas. It usually occurs in white males in the fifth or sixth decade with a history of COPD (especially bullous disease). The natural reservoir is not known. Fifty percent of the patients have no symptoms. Infection, however, commonly mimics pulmonary tuberculosis. The disease is frequently bilateral and more often located in the anterior segments of the upper lobes. The natural course of the disease is to gradually progress with lung destruction. Infections due to M. kansasii usually respond to standard antituberculous therapy. A three drug regimen is usually recommended to include isoniazid, ethambutol, streptomycin or rifampin for a period of 18 to 24-months or 6 months beyond any culture or radiographic evidence of activity. Some studies have yielded a 92% success rate (1,3). The role of surgery appears to be limited to selected patients with localized disease who appear to be medical failures.

MYCOBACTERIUM AVIUM-INTRACELLULARE

This organism was termed the "Battey bacillus" by Runyon after the Battey State Hospital in Georgia. M. avium and M. intracellulare strains resemble each other so strongly that the distinction cannot be made by routine laboratory examinations. Seroagglutination affords the most useful separation in the laboratory, but clinically there is no significant difference between the two organisms anyway. The incidence of pulmonary and extrapulmonary disease secondary to M. avium-intracellulare (MAI) is increasing in North America (13). Unlike M. kansasii, the other most prominent nontuberculous mycobacterium associated with human disease, infections with MAI are as a rule highly resistant to treatment. This constitutes a significant clinical problem, because with the exception of patients with cervical adenitis, the patients that acquire this disease tend to be debilitated and do not tolerate aggressive chemotherapy.

Significant infection associated with MAI results in three distinct types of disease - cervical adenitis, chronic pulmonary disease, and disseminated infection in patients with AIDS. Each is treated differently.

Unlike chronic pulmonary disease and disseminated infection due to MAI, cervical adenitis secondary to MAI tends to occur in immunocompetent hosts, primarily children. The disease process is usually limited, and is cured with surgical excision of infected lymph nodes. As opposed to Mycobacterium tuberculosis, adjunctive chemotherapy is not indicated.

Chronic pulmonary disease due to MAI constitutes a much tougher clinical problem. MAI is a common environmental organism that is frequently recovered from sputum and bronchoscopy specimens. The typical host tends to have local alteration of host defenses (chronic obstructive pulmonary disease, bronchiectasis, or fibrotic disorders (13). These patients tend to be older than patients with M. tuberculosis. The first step in evaluating these patients is determining whether the positive MAI culture represents saprophytic contamination of the airways or true invasive disease. In the patient who is symptomatic from a pulmonary standpoint and lacks cavitation on chest x-ray, a program of intensive bronchial hygiene including smoking cessation, inhaled bronchodilators, broad spectrum antibiotics and chest physiotherapy (if indicated) will result in clearing of MAI from the system in a large number of patients (14). If a patient deteriorates clinically and radiographically despite intensive bronchial hygiene with persistently positive sputum culture for MAI and/or tissue invasion is documented by lung biopsy, chemotherapy should be considered. The American College of Chest Physicians (ACCP) consensus statement recommends the empiric use of a "simple" regimen regardless of susceptibility pattern: 18-24 months of isoniziad, rifampin and ethambutol with an initial two to three month course of streptomycin (13). In contrast to the patient with M. tuberculosis, use of an empiric regimen does not appear to select for further drug resistance and results in sputum conversion in a high percentage of cases (15,16). If the patient fails the empiric regimen or he presents with rapidly progressive, highly symptomatic pulmonary disease (unusual in MAI) more aggressive chemotherapy should be instituted using five to six drugs. The ACCP recommends that agents such as ethionamide, cycloserine or Kanamycin be included in these regimens. In patients with localized disease and adequate cardiopulmonary reserve, pulmonary resection combined with chemotherapy should be considered (13).

A significant number of patients with AIDS will develop disseminated infection secondary to MAI (17). The experience with multiple drug regimens has been disappointing. However, chemotherapy should be offered if the patient is smear positive. Unlike MAI infection, Mycobacterium tuberculosis in AIDS patients is treatable and curable. There are no good data showing that treatment of disseminated MAI in AIDS patients alters survival.

MYCOBACTERIUM SCROFULACEUM

This organism occasionally causes pulmonary disease. It most commonly causes cervical lymphadenitis in children. There is strong circumstantial evidence that the cervical lymph nodes become infected via a pathway originating in the tissues of the mouth and throat. M. scrofulaceum has been isolated from the tonsils and edematous gingiva during the eruption of teeth in children manifesting scrofula. The organism is usually highly resistant to antituberculous drugs *in vitro*. Treatment therefore usually includes surgical resection of all involved lymph nodes.

MYCOBACTERIUM FORTUITUM-CHELONEI

These organisms are characterized by rapid growth in culture, i.e. seven to fourteen days. The disease most commonly consists of soft tissue abscesses and wound infections. Soft tissue infections include post sternotomy wound infections, sternal osteomyelitis, and wound infections following augmentation mammoplasty. Contamination of porcine prosthetic heart valves with *M. chelonei* has also been reported (9,10). Disseminated disease has been described in immunocompromised patients. In none of the cases was a source or cause of the infection identified. All of the patients had numerous sites of cutaneous involvement, manifested by subcutaneous nodules, abscesses, cellulitis, or maculopapular lesions. Deaths in patients affected with *M. fortuitum* or *M. chelonei* have been infrequent, probably reflecting the fact that most infections have involved non-vital areas of skin and soft tissue. The disease is generally self-limited. Deaths have primarily occurred in patients with either endocarditis or sternal wound infections. There is an interesting association between *M. fortuitum* pulmonary disease and achalasia. It is speculated that recurrent aspiration of lipid-containing foods in patients with achalasia predisposes them to an infection with *M. fortuitum* or *M. chelonei*. Diseases associated with pulmonary *M. fortuitum* or *M. chelonei* infection in addition to achalasia include rheumatoid arthritis and ankylosing spondylitis. Both organisms appear to be equally pathogenic. There is a marked difference, however, in susceptibility to antibacterial agents. *M. fortuitum* appears to be much more sensitive to amikacin, doxycycline, and sulfonamides than are isolates of *M. chelonei*. It is recommended that parenteral therapy with amikacin and cefoxitin should be used against *M. chelonei* infection since this organism is usually resistant to both tetracyclines and sulfonamides. Surgical resection may have a role in selected patients. The natural course of pulmonary disease secondary to these organisms is not well known. It does appear however that the pulmonary disease may be stable or very slowly progressive. Therefore, it may be reasonable to follow patients off therapy. Lung tissue histopathologically reveals the prescence of polymorphonuclear neutrophils and microabscesses, and the absence of caseation. This represents a marked contrast to the mononuclear infiltrate and caseating granulomas seen in tuberculosis. Acid fast bacilli are occasionally seen in the center of the microabscesses, but are frequently absent. Thus, in the lung the presence of a dimorphic inflammatory response (i.e. both acute and granulomatous inflammation) in a lesion caused by an acid fast organism is virtually diagnostic of infection due to *M. fortuitum* - *M. chelonei* complex (11).

MYCOBACTERIUM XENOPI

A total of 50 cases of pulmonary disease secondary to *M. xenopi* were reported from 1965 to 1979. There is nothing distinctive about the clinical presentation or the predisposing conditions associated with these infections (3). Patients are often asymptomatic. Chest roentgenograms may reveal nodular lesions as well as cavities in the upper lobe. The organism is found in both hot and cold water taps and water storage tanks. Birds are a probable reservoir. As a rule these organisms are more sensitive to traditional antituberculous therapy than other mycobacteria found in Runyon's Group III (i.e. *M. avium-intracellulare*) (1,12,13).

MYCOBACTERIUM MARINUM

This organism is found in fresh and salt water. Infection is usually manifested as skin lesions with regional adenitis. Most cases are sporadic and associated with fishing, recreation, occupation, or the maintenance of tropical fish aquariums. The organism is often susceptible to rifampin and ethambutol (3).

MYCOBACTERRIUM SIMIAE

M. simiae was originally isolated from a colony of *Macacus rhesus* monkeys in 1965 (14). Unlike other non-tuberculous mycobacteria, this organism is niacin positive. It is rarely associated with disease in humans. The largest study to date is a retrospective study of 24 patients with *M. simiae* isolated from their sputum. Only two of these patients met criteria for infection, three probably had progressive disease, and nineteen had no evidence of pulmonary disease. In disease states, traditional antituberculous therapy if often unsuccessful (15).

MYCOBACTERIUM SZULGAI

This scotochromogen can rarely cause pulmonary cavitary disease, typically in middle-aged men. It is susceptible to several anti-tuberculous drugs including INH, streptomycin, and ethionamide (1,3).

CONCLUSION

The nontuberculous mycobacteria are ubiquitous and infection is probably common. Disease, although relatively uncommon, has a broad spectrum of manifestations. The natural course of pulmonary disease is not necessarily one of continued parenchymal destruction. Vigorous therapeutic measures including multiple drugs and resection should be reserved for those cases demonstrating an unfavorable course. In many cases, observation alone or simple non-toxic drug regimens are appropriate. Perhaps the most difficult problem once disease is diagnosed is identification of patients with a poor prognosis.

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HISTOPLASMOSIS

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Histoplasmosis is a systemic fungal infection caused by *Histoplasma capsulatum*. The organism is a dimorphic fungus that exists in mycelial form in soil and yeast phase in tissue. Infections are acquired by inhalation of soil dust containing infectious microconidia. There is a worldwide distribution in the temperate zones; infection is endemic in the central United States, especially along the Ohio, Mississippi and Tennessee river valleys and the Atlantic seaboard, as well as in South America, Central America and India. It has been estimated that 40 million people in the United States have been infected. The organism's growth is enhanced by the presence of chicken, starling, or bat guano mixed with soil or decaying vegetation. Focal points of infection have been localized in chicken houses, starling roosts, pigeon roosts, hollow trees, and bat-infested caves, attics and roofs. There is no evidence of animal-to-man or man-to-man transmission.

PRIMARY HISTOPLASMOSIS

Primary infection involves essentially the entire population in endemic areas. It is usually asymptomatic. Occasionally acute pulmonary infection is manifested by flu-like illness, cough, chest pain, fever, malaise, headache, anorexia and myalgias. Chest roentgenograms may reveal parenchymal infiltrates with hilar or mediastinal adenopathy. Pleural effusions may rarely be present. Infiltrates may resolve and reappear in other lung fields. Acute cavitation has been seen. Illness is usually self-limited and of short duration. Chest radiograph residua may include multiple small calcified pulmonary nodules and associated splenic calcifications (4). An acute fulminant infection due to inhalation of a large number of organisms can be seen following heavy exposure. Activities such as cleaning out chicken coops, spelunking in caves containing bat guano, or bulldozing starling roosts have been associated with local "epidemics" of acute histoplasmosis (5-8).

RE-INFECTION HISTOPLASMOSIS

Re-infection type histoplasmosis is due to a heavy aerosol challenge in a host previously sensitized to that antigen (hypersensitivity). The process may cause acute, chronic or disseminated histoplasmosis. The incubation period is short, approximately three to five days. Symptoms include abrupt malaise, headache, chills, fever and cough. The process may be severe with patients presenting with ARDS. Chest roentgenograms may be indistinguishable from miliary tuberculosis. There is no lymphadenopathy or pleural effusion. Multiple 1 to 2mm nodules may be seen. Radiographs clear over 3 to 4 months with no calcification (4).

CHRONIC PULMONARY HISTOPLASMOSIS

Chronic pulmonary histoplasmosis is unusual, with an incidence of probably less than 1% of all *Histoplasma* infections. It was initially seen in some patients in tuberculosis sanatoria. The disease complicates pre-existing chronic obstructive pulmonary disease (centrilobular emphysema and bullous disease). The prognosis is primarily related to the severity of the underlying COPD. Symptoms are similar to pulmonary tuberculosis and include malaise, fever, cough and night sweats. Patients may complain of aching chest pain or hemoptysis (33%). Approximately 20% of patients are asymptomatic.

Three clinical and radiologic forms of chronic histoplasmosis have been recognized: pneumonic, persisting cavitary, and late non-cavitary (26). The pneumonic lesion is an interstitial or nodular infiltrate which is usually apical and contains pre-existing emphysematous air spaces. Walls of contiguous bullous spaces are visible radiographically as cyst-like cavities. This form of chronic pulmonary histoplasmosis has a good prognosis with 75% of cases resolving without specific anti-fungal therapy.

Persisting cavitary lesions may be thin-walled (1-2mm) or thick walled (>2mm). According to Dr. Goodwin's experience, approximately 60% of thin wall and 20% of thick wall cavities resolve without specific therapy. Other investigators have not found that such a distinction in prognosis could be made (27). A marching cavity is a thick-walled cavitary lesion which advances down the lung from the apex at a rate of 1-2 cm/year, progressively destroying that lung.

The late non-cavitary lesion is an infiltrate showing evidence of organization and fibrosis. It is not progressive and has a good prognosis even if sputum cultures remain positive for a prolonged period.

DISSEMINATED HISTOPLASMOSIS

Disseminated disease can be classified as severe, moderate chronic, or mild chronic (4). Severe disease is almost always seen in infants or adults who are immunocompromised. It is characterized by marked toxicity with fever, weight loss, and sepsis. Diffuse lymphadenopathy and hepatomegaly are almost always present. Bone marrow suppression is commonly seen, often manifested as pancytopenia. Diffuse lung infiltrates are commonly present.

Moderate chronic disease is subacute in progression with low grade fever and weight loss as the predominant symptoms. Hepatomegaly is usually present and there is a tendency toward focal lesions and organ destruction such as Addison's disease from adrenal involvement, intestinal ulcerations, and less commonly meningitis or endocarditis.

Mild chronic disease is associated with intermittent constitutional symptoms which may be present over a period of many years. The oropharyngeal ulcer is the hallmark of this syndrome.

MEDIASTINAL INVOLVEMENT

Histoplasmosis sometimes presents with unilateral or bilateral enlargement of hilar, mediastinal or intrapulmonary lymph nodes. This form is particularly common in children (16). Most patients are asymptomatic and develop nodal calcification. Extrinsic pressure of enlarged nodes on the airways, however, may cause obstruction resulting in distal infection or atelectasis. This most commonly involves the right middle lobe bronchus. Calcified lymph nodes may erode into the bronchial lumen causing broncholithiasis. Symptoms include cough and hemoptysis. The patient may note cough productive of gravel-like sputum.

Pulmonary infection may extend into the mediastinal space producing a granulomatous or fibrotic mediastinitis. Pericarditis may occur with calcification of the pericardium or constrictive pericarditis (17,18). Enlarged posterior mediastinal lymph nodes may encroach upon the esophagus. The superior vena cava may become partially or totally obstructed by enlarged mediastinal lymph nodes leading to the superior vena cava syndrome (19-22). Surgical resection of involved tissue may be curative early in the disease process (23). Occasionally severe mediastinitis with fibrosis results in obstruction of pulmonary arteries and/or veins. Pulmonary hypertension may arise from direct arterial involvement or indirectly as a result of veno-occlusive disease. In patients with fibrosing mediastinitis, extrinsic compression most commonly affects the right paratracheal and subcarinal areas. This reaction does not represent an active infection but rather an exuberant host response to residual antigen. In these cases drug therapy is ineffective.

HISTOPLASMOMA

Histoplasmomas are relatively common. They are usually solitary and sharply circumscribed. Frequently the lesions are noted in the lower lobes, often with satellite lesions nearby. Many calcify producing the "target" lesion that is virtually pathognomonic of granulomatous disease. Serial roentgenograms over months or years may reveal moderate growth and the nodules may cavitate. Fungal stains usually reveal organisms but cultures are sterile (24,25). Medical treatment is not indicated after surgical excision of a solitary pulmonary nodule discovered to harbor *Histoplasma* organisms.

HISTOPLASMOSIS AND AIDS

AIDS patients with histoplasmosis frequently develop severe disseminated disease with associated fungemia. Disease relapse is common in those patients fortunate enough to complete a course of amphotericin at 35 mg/kg. Ketoconazole may have a role as *maintenance therapy* in these patients. However, relapses have been reported to occur even while taking this drug (34,35,39).

DIAGNOSTIC TESTS

Sputum cultures are useful in the diagnosis of histoplasmosis since the organism is not found as normal flora. Sputum cultures are positive in about 10% of patients with acute disease, 50-70% of those with cavitary disease, and 75% of those with disseminated disease who have lung infiltrates. Wright stain or cultures of blood are positive in up to 75% of those with the severe form of dissemination.

The histoplasmin skin test is useful only as an epidemiologic tool as there are a significant number of false negatives, particularly in disseminated disease, and it tends to wax and wane even in endemic areas. The skin test will cause a significant rise in complement fixation titer in 15-25% of patients.

The complement fixation serology is reported out as a mycelial antigen titer and a yeast antigen titer. The mycelial antigen titer is highest in cavitary disease and the yeast phase titer is highest in acute disease. At a titer of 1:8 for either antigen the sensitivity is 80-95% in acute or cavitary disease but only 60% in disseminated disease. For the yeast phase antigen, however, specificity is low (about 60%), with false positives being due to cross reactions with other mycoses or to simply living in an endemic area. If the mycelial phase titer is positive at 1:8, specificity is 95%. Equal specificity is obtained with the yeast phase titer if it is present at $\geq$1:32 or if a 4 fold rise is documented (4, 26-28, 31, 32).

An agar gel immunodiffusion assay is available, which if positive for the M band has approximately equal sensitivity and specificity to a yeast phase CF titer of 1:8. If the immunodiffusion test is positive for the H band, it has a sensitivity and specificity approximately equal to a yeast phase CF titer of 1:32.

A very sensitive assay for detection of histoplasmosis antigen in serum and urine of patients with disseminated disease has been reported but is not yet widely available (28).

A radioimmunoassay and an enzyme immunoassay have recently been reported to be 100% sensitive for chronic pulmonary disease, although specificity was less than with complement fixation. Further clinical studies will be necessary to validate the clinical usefulness of these newer assays (29,30).

Angiotensin converting enzyme levels are elevated in 15-25% of patients with acute histoplasmosis, who may present with hilar adenopathy which mimics sarcoidosis (33).

THERAPY

In acute symptomatic histoplasmosis, simple rest seems to decrease the severity and shorten the duration of illness. Premature increase in physical activity may lead to exacerbations of the disease (4). If the illness is unusually severe or persists longer than 2-3 weeks, a short course of amphotericin should be given (500-1000 mg) to prevent dissemination and shorten the duration of illness (36). It has been suggested that ketoconazole may be useful in this situation but there are no trials demonstrating efficacy in the acute form of disease. In rare cases with marked toxicity and hypoxemia, steroids have been used successfully to decrease the severity of illness while amphotericin is being initiated (4,37).

In chronic pulmonary histoplasmosis, pneumonic lesions may be treated with rest and close follow-up. Persisting thin-walled cavities ("persisting" defined as present longer than 2-3 weeks) (26) should be treated with amphotericin (2 gms), or 6 months or more of ketoconazole The most effective therapy for thick-walled cavities is resection. However that is rarely possible in patients with severe underlying COPD. In these cases 2-4 gms of amphotericin is usually given, though the failure rate has been reported to be high (>40%) (26). These patients may need repeated courses of therapy. Ketoconazole has also been used successfully in thick-walled cavities (38). Late, non-cavitary lesions do not require anti-fungal therapy. After successful therapy, most patients with chronic pulmonary histoplasmosis will die of their COPD. Twenty per cent of patients will get new pneumonic lesions at an average of 5 years after their initial lesion, and 10% of patients will die with or from active histoplasmosis (26).

All forms of disseminated disease must be treated with antifungal chemotherapy. In severe disease amphotericin (35/mg/kg) is the treatment of choice while moderate or mild chronic disease may be treated with either amphotericin or ketoconazole.

If ketoconazole is used, it should be given for at least 6 months at a dose of 400-600 mg/day. Of 99 patients studied and treated with ketoconazole, approximately 80% demonstrated clinical and serologic improvement. However, relapse rate seemed higher when compared to patients treated with amphotericin.

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BLASTOMYCOSIS

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GENERAL

Blastomycosis refers to the human illness caused by Blastomyces dermatitidis. It was previously referred to as North American blastomycosis, however it has recently been well documented in South America, Africa and Asia. It is a thermally dimorphic organism existing in a mycelial phase in soil and in a yeast phase in the mammalian host.

EPIDEMIOLOGY

Although an endemic area has been difficult to define due to lack of a reliable skin test, the western border appears to stretch from Minnesota to east Texas. From there the range extends east to the Atlantic, north to Canada, and south to the Gulf states. In contrast to histoplasmosis, it is distributed as scattered microfoci rather than widely dispersed throughout its endemic area. Like histoplasmosis, it has been associated with areas of bird droppings.

Dogs are susceptible to the disease and canine outbreaks often parallel human cases. Occurrence of canine and human disease in the same household led to the revelation that leisure activities such as hunting and camping in an infested area were the common denominator of many small epidemics. Accordingly, with an incubation period of 4-8 weeks, the peak season for blastomycosis is winter. The male to female ratio is about 9:1.

The route of entry is respiratory as the organism is aerosolized when infested areas of soil are disturbed. Except for rare cases of conjugal or percutaneous transmission, there is no man to man or animal to man transmission. All ages and races are equally susceptible.

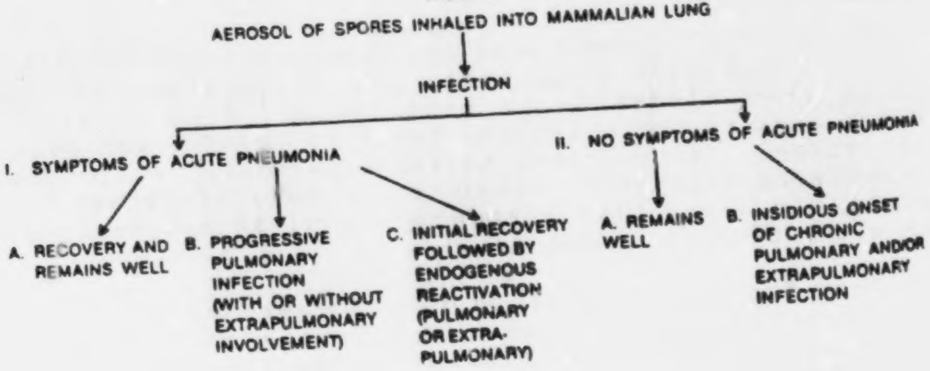
PATHOGENESIS

In the alveolus the arthrospore converts to the yeast form and begins to reproduce by budding. A mixed neutrophilic and mononuclear cell infiltrate leads to an area of pneumonitis. Even after granuloma formation, areas of suppuration are histologically seen to co-exist with areas of granulomata. Except for coccidioidomycosis, this property is unique among the mycoses. If cell-mediated immunity develops properly the infection is contained and the infiltrate begins to "round off". Healed areas may be seen as fibrosis or residual "coin" lesions. In some instances, even in apparently normal hosts, the infection is not contained and may spread to skin, bones, GU tract, meninges, upper airway, or adrenal glands.

CLINICAL MANIFESTATIONS

Since the portal of entry is respiratory, the primary infection is pulmonary. Symptoms may range from none to respiratory failure with ARDS and dissemination (See Table 2 below). Probably a third to one-half of infected patients become symptomatic, although the lack of a reliable skin test reduces this estimate to the level of educated guesswork. Acute symptomatic cases may masquerade as a viral syndrome with sudden onset of fever, arthralgias, myalgias, headache, cough, pleuritic chest pain, and photophobia. Erythema nodosum, in contrast to coccidioidomycosis, is uncommon and is not predictive of a good recovery.

TABLE 2


AEROSOL OF SPORES INHALED INTO MAMMALIAN LUNG
INFECTION
I. SYMPTOMS OF ACUTE PNEUMONIA
II. NO SYMPTOMS OF ACUTE PNEUMONIA
A. RECOVERY AND REMAINS WELL
B. PROGRESSIVE PULMONARY INFECTION (WITH OR WITHOUT EXTRAPULMONARY INVOLVEMENT)
C. INITIAL RECOVERY FOLLOWED BY ENDOGENOUS REACTIVATION (PULMONARY OR EXTRA-PULMONARY)
A. REMAINS WELL
B. INSIDIOUS ONSET OF CHRONIC PULMONARY AND/OR EXTRAPULMONARY INFECTION

(from Sarosi and Davies[19])

There is no characteristic chest radiograph pattern; infiltrates have been described as segmental, lobar, diffuse nodular, and mass-like, but hilar/mediastinal adenopathy seems to be uncommon. Some feel that the lower lobes are the most common sites, particularly the superior segment of the right lower lobe.

Probably, most cases with acute symptomatic involvement have spontaneous resolution of infiltrate and symptoms over 4-6 weeks. However, months to years later the disease may endogenously reactivate in the lungs or at distant sites. The disease may also be manifested as a slowly progressive form with constitutional symptoms over a period of months. Slowly progressive disease is also associated with a variety of radiographic patterns including cavitary, pneumonic, or miliary, and it is commonly accompanied by extra-thoracic involvement.

Pleural involvement is common in blastomycosis with one series reporting radiographic evidence of it in 88% of cases. In addition, the severity of pleural involvement may be of benefit in prognostication, in that 40% of those with >1.5 cm of pleural effusion or reaction died of the disease or had relapse.

Compared to histoplasmosis and coccidioidomycosis, disseminated disease is very common in blastomycosis and is not associated with the same unfavorable prognosis. Skin is the most common site of dissemination with face and trunk being favored sites. Maculopapular lesions are seen to evolve into verrucous, ulcerating granulomas. Bone is the next most common site, usually vertebrae and ribs. Characteristically, bone involvement involves adjacent soft tissue producing an abscess. Other sites of dissemination are listed above under "Pathogenesis". Only a small number of immunosuppressed patients with blastomycosis have been reported. They accounted for a very small percentage of cases in a consecutive series and did not seem prone to a more virulent course if the diagnosis was made and treatment started within a reasonable period of time.

DIAGNOSIS

The organism can be readily isolated from body fluids or tissue and is seen on H&E or GMS stains, but PAS staining is best as it reveals the characteristic multiple nuclei. Morphologically it is a large, broad based budding yeast with a doubly refractile cell wall. Sputum KOH will reveal the organism in about 70% of patients with pulmonary involvement. Prostatic massage reveals unsuspected GU tract involvement in as many as 33% of patients.[10]

The blastomycin skin test is unfortunately not very useful. Reports of its sensitivity have ranged from 0-80%. Positivity is short lived and there is a very high incidence of false positives due to histoplasmin sensitivity.

In the past, complement fixation has not been very useful either. However, the CDC and a few other institutions now have a CF assay to a purified A antigen which appears to be ≥70% sensitive and 85-95% specific. In addition to CF, three other methods are used for serodiagnosis. RIA is about 75% sensitive and 80% specific at a titer of ≥1:16, but is also not widely available at the time of this writing. Immunodiffusion by a currently available commercial kit (Meridian Diagnostics) has been reported as 17% sensitive and 100% specific. However, the CDC and a few other institutions have performed immunodiffusion using the purified A antigen and have reported a sensitivity of 88% for disseminated disease and 33% for localized pulmonary disease, again with 100% specificity. Enzyme immunoassay may be the most useful of the available serologic tests, having a sensitivity of 85-100% and specificity of about 85% at a titer of 1:8 to 1:16. However there was a very high incidence of cross reactions in patients who had histoplasmosis, and since histoplasmosis is about 10 times more common than blastomycosis, a positive EIA would be more likely to represent infection with the former. In one study a titer of $\geq$1:64 was strongly associated with dissemination although a rising titer was not predictive. Immunodiffusion may be used for confirmation because of its high specificity. EIA positivity may persist for up to 12 months.

TREATMENT

There is still much controversy on the issue of treatment of acute cases. Sarosi and Davies, who have published extensively on blastomycosis, feel that in cases where disease is limited to the lung, with stable or improving clinical and radiographic features, the patient can be closely observed. Treatment would be reserved for those displaying any signs of clinical or radiographic worsening. They do advocate treatment if the patient could not be trusted to comply with close follow-up. Others advocate treatment for all cases of infection because of the possibility of late endogenous reactivation. All cases of dissemination to extra-thoracic sites must be treated systemically.

The gold standard of therapy remains amphotericin B, 2 gm over 13-20 weeks. However, several studies have now shown that in a dose of 400-800 mg/day for $\geq$ 6 months, ketoconazole is very effective in patients whose clinical condition is stable(85-100% cure). Any patient who is not clinically stable, who is immunocompromised, or who is found to have meningeal involvement should be treated with amphotericin.

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COCCIDIOIDOMYCOSIS

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Coccidioidomycosis is a very common infectious disease with more than 100,000 cases reported each year in the United States. The disease is endemic in the Southwestern United States and Northern Mexico in the Lower Sonoran Life Zone. These areas have predominantly semi-arid, hot climates with a short rainy season. Several cases have been reported, however, from non-endemic regions of the United States as well as Canada, Europe, Australia and Japan (1,2,3). The disease is known by other names including San Joaquin fever, valley fever, desert fever, desert rheumatism, valley bumps, coccidioidal granuloma, the bumps or simply cocci. The disease was first described in 1892 in an Argentine soldier (4). In 1896 the organism was named Coccidioides immitis (5).

Coccidioides immitis is a dimorphic fungus. In the soil phase it germinates to arthrospores which are hardy, resistant to drying, and highly infectious. The arthrospores can cause infection in laboratories. The organism assumes spherule morphology in the tissue phase. Each spherule contains endospores that are seen on GMS or PAS staining. Spherules may occasionally be seen upon examination of body fluids, sputum, pus, or cutaneous exudates by utilizing ten percent potassium hydroxide. The spherules are not infectious and no person-to-person spread has been reported. The lung is the most frequently affected organ and represents the portal of entry by inhalation of arthrospores. A characteristic appearance on biopsy is the simultaneous presence of granulomas with varying degrees of caseation and suppurative areas with micro-abscesses.

DIAGNOSIS

Sputum culture of Coccidioides immitis is diagnostic for disease (6). Sputum KOH stains often reveal spherules. Delayed skin tests (coccidioidin) develop in 95% of patients within four weeks of symptoms (7). The skin test may, however, reflect past infection. Coccidioidin is manufactured from a filtrate of a broth culture of Coccidioides immitis. One tenth cc of 1:100 dilution is injected intradermally. A positive reaction is defined as 5mm or more of induration when read at 24-72 hours. Skin test reactivity may be lost with dissemination. The skin test does not evoke a complement-fixation antibody response but may elevate histoplasmal and blastomycosal antibody titers (8,9). The spherulin skin test is a soluble lysate of the tissue-phase spherules. It detects approximately 33% more cases of primary cocci than coccidioidin and is used in clinical situations consistent with primary cocci when the coccidioidin skin test is negative (10,11).

There are two standard tests used in the serological diagnosis of coccidioidomycosis, tube precipitins and the complement fixation test. Precipitins are IgM antibodies that rise very rapidly in the early stages of clinical illness (seen within 7-28 days in 90% of patients). After four weeks the tube precipitin antibodies decrease rapidly and are found in only 10% of patients at 4 months (12). The complement fixation test measures IgG antibodies. At four weeks approximately 50% of patients are positive. At eight weeks, 90% are positive. Dissemination is usually reflected by complement fixation titers greater than 1:16 to 1:32, but it must be kept in mind that the relationship between risk of dissemination and titer is based on Dr. Smith's original data and that correlation of titers between different laboratories is poor. Falling titers with therapy indicate improvement. Patients with chronic cavitary disease often have titers less than 1:8. An elevated complement fixation titer in the CSF is virtually pathognomonic for meningeal spread (13,14).

Two other procedures used primarily for screening are the latex particle agglutination test and the agar-gel immunodiffusion assay. The latex particle agglutination test measures IgM. It is less expensive, simpler and more rapid than the tube precipitins, but has a 6-10 percent false positive rate. A positive test should be confirmed by tube precipitins (15,16). The agar-gel immunodiffusion assay measures IgG. It is an especially important test in serum or CSF that is contaminated or has anti-complement activity (17).

PRIMARY PULMONARY COCCI

Sixty percent of patients with primary pulmonary coccidioidomycosis are asymptomatic (7,18). Approximately 40% of the patients experience a flu-like, self-limited illness with fever, headache, chills, nonproductive cough and chest pain. The illness is often mistaken for atypical pneumonia. Ten to twenty percent of the patients present with "acute valley fever" with erythema nodosum or erythema multiforme, sterile polyarthritis, pleuritis or pericarditis. Serositis is thought to be immune-complex related. Erythema nodosum has a predilection for white females (18,19). The protective value of erythema nodosum in primary cocci is incomplete as a number of patients have developed dissemination despite antecedent "valley fever" (8). The most common skin manifestation in primary pulmonary cocci is toxic erythema, a diffuse maculo-papular rash that occurs in approximately 20% of the patients (20,21). Forty to seventy percent of patients with primary pulmonary cocci will have sputum culture positivity. Ninety-five percent of the cases are self-limited with complete resolution both clinically and radiologically within 6-8 weeks of clinical onset. Residual pulmonary manifestations may include a coccidioidoma or a peripheral cocci cavity.

Chest roentgenograms may reveal waxing and waning infiltrates (usually lower lobe, occasionally with acute cavitation). Hilar adenopathy, often bilateral, is seen in approximately 20% of patients (8). Paratracheal or mediastinal adenopathy may indicate impending dissemination. Pleural involvement is common with pleural effusion noted in approximately 20% of cases. The effusion is most likely secondary to contiguous spread from an ipsilateral pneumonitis. Cocci is rarely recovered from the pleural fluid although granulomata are frequently observed on parietal pleural biopsy specimens (22).

CHRONIC PROGRESSIVE COCCIDIOIDAL PNEUMONIA

Chronic progressive coccidioidal pneumonia (CPCP) occurs in fewer than 1% of patients with coccidioidomycosis. Instead of experiencing a self-limited illness these patients often remain ill with persistent fever, prostration, chest pain, productive cough and occasional hemoptysis. The disease clinically and radiographically closely mimics pulmonary tuberculosis or histoplasmosis. Sputums are chronically positive for Coccidioides immitis. The disease tends to be relatively indolent with long delays in diagnosis, often greater than two years. Serum antibody titers are usually high, often in the dissemination range. Chest roentgenograms are variable but often reveal biapical fibronodular lesions and multiple cavities. As with disseminated coccidioidomycosis, CPCP occurs more frequently in Filipinos and other Orientals. Evaluation should include lumbar puncture with CSF culture and serologies, fungal cultures of any skin lesions, and biopsy and culture of other organs including liver and bone marrow. Urine cultures may be positive. Therapy with amphotericin B in doses of 30 mg. per kilogram or more generally results in an impressive clinical response. There may be dramatic chest x-ray resolution, and sputum cultures usually become negative (23,24).

MILIARY PULMONARY COCCIDIOIDOMYCOSIS

Miliary pulmonary coccidioidomycosis usually presents as a complication of primary cocci and results in high morbidity and mortality (25). It has been reported in approximately 4% of hospitalized patients with primary cocci (26). The process results from massive, blood-borne dissemination to all lung fields and is associated with underlying disease states such as diabetes mellitus and immunosuppression. It occurs more frequently in Filipinos and closely resembles miliary tuberculosis (27). Sputum cultures are positive in fewer than 40% of cases. The complement fixation titer may be less than dissemination range. The mortality rate approaches 50% despite prompt therapy with amphotericin B (28).

CAVITARY COCC[illegible]IOIDOMYCOSIS

Primary coccidioidomycosis may be associated with acute cavitation within parenchymal infiltrates. Persistent cavities tend to be single and peripheral with approximately 70% noted in the upper lung fields. The majority of the cavities are between 2 and 4 cm. Cavities are usually thin-walled but may occasionally be shaggy with air-fluid levels. Approximately 50% of these cavities close spontaneously within a two year period (13,26). Most nonresolving cavities remain static without symptoms or complications and are rarely associated with dissemination. Seventy percent of patients with cavities are skin test positive but 75% have complement fixation titers less than 1:4 (29). Sputum cultures may be persistently positive for *Coccidioides immitis*. Complications of cavitary coccidioidomycosis include secondary colonization by *Aspergillus* or infection by pyogenic bacteria, subpleural cavity rupture, and hemoptysis (30).

Indications for surgery include a rapidly expanding cavity with risk of rupture, bronchopleural fistula, symptomatic mycetoma, and serious or persistent hemorrhage (26). Other possible indications include a cavity greater than 6 cm., pyogenic cavity, high risk patient (diabetes, pregnancy), or high complement fixation titers (31). Surgery in unruptured cavitary disease is associated with new cavity or bronchopleural fistula formation in 5-30% of patients (1-3% incidence without surgery)(13). Perioperative chemoprophylaxis with amphotericin B is controversial (26) but is usually advised to decrease the incidence of postoperative infectious complications. Preoperative and postoperative amphotericin B is indicated in patients with serious underlying disease or in patients with a large expanding cavity and high complement fixation titers. The usual recommended postoperative amphotericin B dose is approximately 500 mg. given over a 14 to 21 day period (32).

COCCIDIOIDOMAS

Coccidioidomas usually present as asymptomatic solitary pulmonary nodules. Tomography may reveal calcification within the nodule. Previous chest roentgenograms should be obtained if at all possible. Most patients are skin test positive with low complement fixation titers. If resected many of the granulomas will have *Coccidioides immitis* identifiable in the center of the lesion. No antifungal therapy is indicated following surgical resection (28).

DISSEMINATION

Dissemination is estimated to occur in approximately 0.5% of symptomatic patients. There is increased susceptibility in non-whites (Filipinos and other Orientals, American blacks, Mexican Americans, and native Americans). Dissemination usually occurs early in the infection and is more likely in the setting of immunosuppression or pregnancy (especially when the infection is acquired in the latter half of pregnancy) (33). Dissemination should be considered when there is persistent fever and toxicity beyond four weeks. As previously mentioned, a complement fixation titer greater than 1:16 suggests dissemination. Chest roentgenograms may be normal, or reveal a miliary pattern, and/or hilar and paratracheal adenopathy. Untreated dissemination is associated with a fatality rate in excess of 50% within three years (34).

Osteomyelitis occurs in one-half of the cases. The bone lesions are usually osteolytic. Meningitis occurs in approximately 20% of patients with dissemination. Cerebrospinal fluid examination reveals increased lymphocytes, elevated protein, and decreased glucose, with a positive CSF complement fixation titer occurring in 75% of cases. The coccidioidin skin test is typically negative (35).

AIDS AND COCCIDIOIDOMYCOSIS

For AIDS patients living in Arizona, coccidioidomycosis has been particularly devastating, as reported in a recent series from Tucson. In those AIDS patients, there was a 27% annual incidence of coccidioidomycosis. Extensive pulmonary involvement and dissemination occurred in all patients and all died within 14 months of the diagnosis of coccidioidomycosis. Complement fixation titers were positive in five out of seven at the time of presentation. Although amphotericin was initially effective in reducing infiltrates and symptoms, it was not curative and all patients who responded initially had relapse (45).

THERAPY

In primary pulmonary coccidioidomycosis, therapy is indicated only when symptoms are severe or risk factors for dissemination are present. Standard treatment for this form of the disease has been 500-1000mg of amphotericin. If skin test reactivity fails to develop or there is a progressive rise in CF titer suggesting imminent dissemination, then longer therapy is indicated. Ketoconazole may eventually play a role in this clinical setting, but as yet this has not been defined.

In persistent or progressive pneumonia, 1-3 gm of amphotericin should be given over 1-3 months, or longer if necessary. If fibronodular scarring develops, lasting eradication of organisms is unlikely. Patients with cavitary disease are candidates for therapy with 1-3 grams of amphotericin only if symptoms are prominent and cavitary walls are thick. Indications for surgical intervention for cavitary disease are described above.

Disseminated disease is the clearest indication for therapy, with the goals of therapy being three-fold: marked clinical improvement, healing of all apparent lesions, and reduction in CF titer to lowest possible level (usually at least a 4-fold decline). Areas of localized disease should be resected whenever practical. After 2 gms of amphotericin, intermittent therapy may be needed thereafter to maintain remission. Meningeal infection requires intrathecal and intravenous amphotericin and may require years of treatment to maintain remission. A recent report advocates use of higher intrathecal doses than have been used routinely in the past, in order to increase survival (26, 36-38, 46-48).

The most experience with ketoconazole has been in the treatment of coccidioidomycosis. In a review of five large studies it was noted that the majority of patients with non-meningeal disease improved but few were cured (46). The minimum course of therapy should be 400 mg/day for 6 months. The advantages of ketoconazole are ease of administration and safety over the long periods of treatment that many patients require, thereby permitting suppression of the patient's disease and allowing him to live relatively unencumbered by the therapy. Ketoconazole was not effective for vertebral osteomyelitis, was more effective in infiltrative than cavitary pulmonary disease, and was most effective for cocci skin lesions (41-43,46).

A recent study evaluated the pharmacokinetics of ketoconazole in CSF and the clinical response to doses of 800-1200 mg/day in six patients with CNS fungal disease (five patients with cocci). CSF concentrations of ketoconazole varied directly with those in serum and with CSF protein level. Clinical results suggested that treatment with 800 mg ketoconazole plus intraventricular amphotericin B, or 1200 mg ketoconazole alone is effective. When intrathecal therapy is hazardous or is refused by the patient, treatment solely with ketoconazole in high doses may be justified (44).

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ASPERGILLOSIS

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Aspergillosis refers to a variety of diseases caused by members of the genus *Aspergillus*. *Aspergillus fumigatus* and *Aspergillus niger* are the most common species associated with disease in man. *Aspergillus* species are ubiquitous in nature and occur as saprophytes in the upper respiratory tract and as contaminants in the laboratory. They are found in soil, decaying vegetation and organic debris, and are often part of the normal oral and sputum flora. The *Aspergillus* species cause numerous syndromes in man including allergic bronchopulmonary aspergillosis, extrinsic alveolitis, aspergilloma, invasive pulmonary aspergillosis, disseminated aspergillosis, and chronic necrotizing pulmonary aspergillosis. *Aspergillus* species may colonize the respiratory tract of healthy people. One study revealed colonization in approximately 16% of normals (1). Conclusive diagnosis of aspergillosis is difficult and often requires microscopic demonstration of tissue invasion. Tissue reaction to aspergillosis consists primarily of granuloma formation. Tissue invasion rarely occurs in previously healthy patients.

PULMONARY MYCETOMA

A mycetoma is a conglomeration of intertwined fungal hyphae, fibrin, mucus, and cellular debris within a pulmonary cavity. Almost invariably the underlying cavity can be ascribed to other causes such as bronchiectasis, sarcoidosis, tuberculosis, histoplasmosis, bronchial cyst, chronic bacterial abscess, or carcinoma (3-12). Histologic examination of the cavity wall does not demonstrate invasion by the hyphae (6). Sputum in patients with mycetoma rarely contains the organism. The aspergillus skin test is positive in approximately 20% of patients and precipitins are present in nearly 100%. The fungal ball occurs more commonly in the upper lobes and frequently is associated with adjacent pleural thickening. A characteristic feature of mycetoma is the movement of the fungal ball within the cavity which can be seen on x-ray or fluoroscopy when the patient changes positions (i.e. left or right lateral decubitus position). Mycetoma may be due to other organisms such as *Candida albicans*, *Streptomyces spp.*, *Allescheria boydii*, or *Nocardia asteroides*. Hemoptysis, sometimes massive, has been reported in 45 to 70% of cases (3, 6, 13). In patients with recurrent bleeding, lobectomy should be considered as death from asphyxiation or exsanguination can occur (13-18). Since most patients with mycetomas are asymptomatic and local invasion or systemic dissemination is rare, therapy is infrequently required.

Intravenous administration of amphotericin B is no more effective than a pulmonary toilet regimen in the management of mycetomas (19). Intracavitary instillation of amphotericin B may enhance resolution of the mycetoma (20). It is estimated that 7-10% of mycetomas lyse spontaneously (21,22).

BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

Allergic bronchopulmonary aspergillosis occurs in patients with long standing atopic asthma. There is frequently a history of progressive recurrent exacerbations of asthma with sputum production occasionally demonstrating brownish bronchial casts. Chest roentgenograms typically reveal changing pulmonary infiltrates, particularly involving the upper lobes, with suggestion of mucoid impaction in the more central segmental bronchi resulting in central bronchiectasis. Distal atelectasis and bronchiectasis may also be seen. Resolution of the lesion leaves cylindrical or saccular dilatation of the bronchi at the site of the mucoid impaction (23, 4). Patients present with fever, cough productive of purulent sputum or mucous plugs, and hemoptysis. Dyspnea may be very severe. Peripheral eosinophilia and elevated serum IgE levels are characteristically seen in ABPA. Most patients manifest a positive aspergillus skin test, typically with an immediate (Type I) reaction that is IgE mediated and a delayed or Arthus reaction at 5 to 6 hours. Aspergillus IgG precipitins can be identified in approximately 70% of the patients (24). Inhalation of aspergillus extract can result in decreased forced expiratory volume (23). Examination of mucous plugs and sputum typically reveals the organism. Treatment with corticosteroids frequently results in significant clinical improvement. Many patients require prolonged low-dose corticosteroid therapy to prevent recurrent symptoms.

INVASIVE PULMONARY ASPERGILLOSIS (IPA)

Invasive pulmonary aspergillosis is a necrotizing pneumonitis that can be caused by several *Aspergillus* species. Histopathologic examination typically reveals fungal invasion of the pulmonary vasculature with resultant hemorrhagic infarction. The disease typically occurs in the immunocompromised host and is often unrecognized antemortem. Methenamine silver stain of tissue sections from patients with aspergillosis reveals broad, septate hyphae with repeated branching at 45 degrees. Clinical states associated with invasive aspergillosis include leukemia, lymphoma, use of corticosteroids or other immunosuppressive drugs, renal and cardiac transplants. Predisposing factors for IPA include: 1) high-dose steroids, 2) cytotoxic chemotherapy, and 3) leukopenia. In a recent prospective study, 108 consecutive patients were evaluated in whom *Aspergillus* species were isolated from respiratory secretions. IPA was not demonstrated in non-immunosuppressed patients or in patients with solid tumors in the absence of neutropenia. However, isolation of A. fumigatus or A. flavus from the respiratory tract of a patient with leukemia and/or neutropenia was highly predictive of invasive infection (25). Empiric amphotericin B therapy without tissue confirmation should be considered in this subgroup. There have only been 15 documented cases of invasive pulmonary aspergillosis in normal hosts (26-28). Infection in the immunocompromised host is often preceded by Pseudomonas aeruginosa infection (24). The portal of entry for the fungus is probably via tracheobronchial aspiration or nasopharyngeal colonization. Physical findings are nonspecific and include fever, rales or rhonchi, and mucosal ulceration anywhere along the gastrointestinal tract. The ulcerations may cause major gastrointestinal hemorrhage. In leukopenic leukemic patients, surveillance nasal cultures positive for Aspergillus frequently antedate development of frank invasive pulmonary or disseminated aspergillosis (30).

Chest roentgenograms may reveal pulmonary nodules with cavitation, diffuse bilateral pulmonary consolidation or the abrupt development of large wedge-shaped, pleural-based lesions mimicking pulmonary infarction. Invasive pulmonary aspergillosis should be suspected in the immunocompromised host with roentgenographic evidence of nodules, cavitary lesions, or infiltrates that are unresponsive to treatment with broad spectrum antimicrobial agents (29). Recently, CT scan evidence of a "halo sign" or zone of lower attenuation surrounding a pulmonary mass in adult leukemic patients strongly correlated with IPA. CT established the presence of IPA before plain films in two patients (31).

Histopathologic specimens often reveal endobronchial hyphal proliferation, invasion of pulmonary arterioles, and ischemic necrosis of small areas of the lung. In approximately 10 to 25% of patients with invasive pulmonary aspergillosis, extrapulmonary dissemination is found at autopsy (29,31). Paranasal sinuses, the middle ear, and mastoid air cells are frequent sites for disseminated Aspergillus. Rhinocerebral aspergillosis is frequently overlooked.

The prognosis for invasive aspergillosis correlates with early diagnosis and institution of therapy, induction of remission of the underlying disease, and reversal of chemotherapy-induced bone marrow suppression (33). Patients with invasive pulmonary aspergillosis complicating renal or cardiac transplantation have a relatively lower mortality (approximately 25%), as compared to the 70% mortality rate seen in patients with associated hematopoietic or lymphoreticular malignancies (26,28,30,31,33-35).

Aspergillus has been recovered from the sputum in fewer than 10% of patients with invasive pulmonary aspergillosis. As noted, isolation of aspergillus from surveillance nasal cultures of immunocompromised patients correlates with concurrent or subsequent invasive pulmonary aspergillosis. Negative nasal cultures however do not preclude the diagnosis of invasive pulmonary aspergillosis. A definitive diagnosis requires histopathologic evidence of parenchymal invasion of lung tissue usually obtained via open lung biopsy. Bronchial washings or brushings that are culture or GMS positive can only be interpreted as presumptive evidence of invasive pulmonary aspergillosis. In patients with invasive pulmonary aspergillosis serum precipitins are undetectable or low and skin test and serologies are generally negative.

Invasive pulmonary or disseminated disease should be treated with amphotericin B. In immunocompromised patients it is often wise to reduce steroid and cytotoxic chemotherapy if possible. Limited thoracotomy with wedge resection may be therapeutic in patients with relapsing invasive pulmonary aspergillosis despite appropriate medical regimens (29). The use of 5-fluorocytosine (5-FC) in patients with IPA is controversial. Bone marrow toxicity can occur at relatively high dosage.

CHRONIC NECROTIZING PULMONARY ASPERGILLOSIS

Chronic necrotizing pulmonary aspergillosis is defined as a chronic, indolent, necrotizing infection of the lungs caused by a member of the *Aspergillus* species. The disease can be diagnosed by the presence of invasive branching septate hyphae demonstrated on lung biopsy with cultures confirming the presence of *Aspergillus* species, or by the clinical criteria of numerous positive cultures for *Aspergillus* species with clinical resolution following antifungal therapy. Other causes of chronic infiltrative processes such as carcinoma, and anaerobic or tuberculous infection must be excluded. Most patients are 35-60 years old, have been ill from 1 to 12 months at presentation, and have a history of previous lung disease. Symptoms include fever, cough and sputum production, and weight loss. Chest roentgenograms frequently reveal pulmonary infiltrates with parenchymal necrosis, predominantly in the upper lobes. Mycetoma formation may occur in up to one-half of the patients. Serum precipitins are universally positive and leukocytosis almost invariably occurs with white blood cell counts in the range of 12,000 to 15,000. Histopathologic examination reveals invasive branching septate hyphae with an acute inflammtory infiltrate. The illness is indolent with recurrent fever and weight loss over a period of months to years. The disease tends to spread to contiguous structures such as the pleural space and chest wall, as well as to nearby lung. Distant spread has not been described. Treatment with amphotericin B often results in significant symptomatic improvement. Chest roentgenograms may remain stable. Surgical complications may be high with empyema, recurrent lung abscess, and bronchopleural fistula being reported (39,40).

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PULMONARY CRYPTOCOCCOSIS

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GENERAL

Cryptococcosis, known previously as torulosis or European blastomycosis, is caused by Cryptococcus neoformans. It has a worldwide distribution, growing most readily in bird excrement, particularly pigeon droppings. The route of entry is known to be respiratory, but it is unclear what morphologic form the organism assumes during transmission.

On histopathology Cryptococcus is seen as a narrow based budding yeast. It is easily distinguishable from other fungi by its polysaccharide capsule which serves to resist phagocytosis. The organism stains well with mucicarmine, GMS, and PAS, but not with H&E. Lesions are initially mucinous and later become granulomatous. In the compromised host, however, gelatinous masses of organisms may form with little or no inflammatory component.

The organism is trophic for the CNS probably for several reasons, but the most important one appears to be the deficiency of complement in CSF. Lung infiltrates are present in only 10-40% of diagnosed cases of cryptococcosis (5).

RISK FACTORS

Risk factors for cryptococcosis in approximate decreasing order of relative risk are: (1) organ transplantation, (2) lymphoreticular cancer, (3) AIDS, (4) collagen vascular disease, (5) hypercortisolism - exogenous or endogenous, (6) diabetes, and (7) sarcoidosis. Cryptococcosis is the most common systemic mycosis in organ transplant patients, although the majority of cases overall are seen in lymphoreticular cancer victims (1). Clearly, defective cellular immunity is the major predisposing factor, although recently a patient with normal cell mediated immunity and hypogammaglobulinemia was reported with disseminated cryptococcal disease (28). Immunocompromised hosts are now accounting for 50-80% of clinically recognized cryptococcal disease (5,17).

CLINICAL AND RADIOGRAPHIC MANIFESTATIONS

Symptoms of primary infection are most often indolent and non-specific in immunocompetent patients, while immunosuppressed patients may present with rapidly progressive symptoms. In a summary of two large series, the most common symptoms were cough, fever, sputum production, dyspnea, and weight loss (1).

The radiographic patterns which have been seen in cryptococcosis are quite variable. However, changes are usually acute or subacute, so that calcification is notably absent, and pulmonary fibrosis is uncommon. Peripheral nodule(s), often subpleural, account for most of the lesions in normal hosts but are also seen not uncommonly in abnormal hosts (5). Other patterns which have been described include mass lesions, cavitary infiltrates or masses, pleural effusion, diffuse interstitial pneumonia (nearly always with disseminated disease in compromised hosts), and segmental or lobar infiltrates. Hilar adenopathy by CXR is very uncommon in normal hosts but may be seen in up to 25% of immunocompromised hosts (5). A chest radiograph pattern suggestive of cryptococcosis is an apparently well defined mass in one view which has the appearance of a more ill-defined infiltrate in the 90 degree perpendicular view (3).

In a review of the literature prior to 1980, Young et al reported cryptococcal pleural effusions to be equally divided between localized and disseminated disease. Effusions, of which 42% were culture (+), were rarely found in the absence of parenchymal lesions. A wide range of cell counts were seen but the differential was always lymphocytic. They performed cryptococcal antigen determinations on two pleural fluid specimens, which were (+) in both. Both of these patients had positive pleural fluid cultures, and one of the 2 had a positive serum antigen (12).

Although rare in normal hosts, reactivation and reinfection have been reported. Saprophytic colonization also occurs - several patients with lung cancer and *Cryptococcus* colonization have been reported (4,10). Thus, a patient with a chest radiograph lesion and sputum cultures positive for *Cryptococcus* should not be presumed to have cryptococcal lung disease. Colonization is most commonly seen in patients with underlying lung disease such as asthma, COPD, or fibrosis.

The clinical course of primary pulmonary cryptococcosis was reviewed by Hammerman et al in a CDC Cooperative Study (6). In 28 cases, most of which occurred in apparently normal hosts, no treatment was given. Of these, 7% went on to develop CNS infection, 3% died of progressive pulmonary disease, and another 7% failed to improve after months of followup and ultimately required therapy. There were 92 cases which had been treated by surgery alone. 3% of these patients went on to develop CNS infection. There was no CXR pattern or symptom complex predictive of dissemination. Duperval in 1977 presented an additional 18 cases with limited (pulmonary) disease who were all doing well with no therapy at 13-44 months after diagnosis (10). Thus, in these series made up primarily of normal hosts, isolated pulmonary disease had a good prognosis without specific anti-fungal therapy.

The prognosis and natural history of pulmonary cryptococcosis in the normal host was differentiated from that of the immunocompromised host in a 1981 report by Kerkering et al (17). Only 1 out of 6 untreated normal hosts disseminated their disease after primary pulmonary infection, but 24 out of 26 compromised hosts did so. In two-thirds of those who disseminated pulmonary cryptococcosis was not diagnosed until after dissemination occurred. Of thirteen compromised hosts in whom pulmonary cryptococcosis was diagnosed at the time of presentation, 4 were treated with 3-6 weeks of amphotericin and flucytosine, and all did well. Nine were untreated and 7 of these disseminated. In over half of the patients who disseminated, the CXR abnormalities resolved or were improving at the time of dissemination. The prognosis of those who disseminated was quite dismal with 50% dying within a week after starting therapy.

AIDS patients have become a frequent source of cryptococcal cases since 1981. Cryptococcosis is the fourth most common life threatening infection in these patients after cytomegalovirus, *Pneumocystis carinii* (PCP), and *M. avium* (21). Most AIDS patients with cryptococcosis present with meningitis but most of these will have evidence of pulmonary involvement at autopsy. It may be the presenting opportunistic infection leading to the diagnosis of AIDS or it may occur late in the course. In this group of patients the most common CXR pattern is an interstitial infiltrate. Concurrent pulmonary infection with other opportunistic pathogens is very common with 5 out of 8 transbronchial biopsies in Gal's series showing PCP as well as *Cryptococcus* (22). (Yield for *Cryptococcus* in this group was 8/8 on lavage, 5/8 on brush and 6/8 on biopsy.) In AIDS patients the organisms may be small and poorly encapsulated, and may be mistaken for the yeast forms of *Candida* or *Histoplasma* on GMS and even on mucicarmine stains. AIDS patients who survive their initial cryptococcal infection (a small minority) often succumb from relapse (22,23).

With dissemination, *Cryptococcus* can infect virtually any major organ. In approximate decreasing order of frequency: (1) CNS - cryptococcomas as well as meningitis; (2) skin - usually a moist shallow ulcer, but different types of lesions have been described; (3) bone - osteomyelitis or bone marrow involvement; (4) eye - endophthalmitis; (5) prostate and GU tract, with 40% of cryptococcemic patients having (+) urine cultures; and (6) assorted others including adrenals, spleen, liver, endocardium, soft tissue and joints.

DIAGNOSIS

In culture, *Cryptococcus* grows relatively rapidly, often within 2-3 days. Subspecies other than *neoformans* should be regarded as saprophytes. Because of the frequency of asymptomatic dissemination, all patients with pulmonary cryptococcosis should be thoroughly evaluated, with cultures of blood, urine, skin lesions if present, and CSF, with cryptococcal antigen determinations on serum and CSF (1). As many as a third of patients without symptoms will have positive CSF(30).

The cryptococcal antigen determination, known as LCAT (Latex Cryptococcal Agglutination Test) has been very successful in the diagnosis and management of patients with meningitis. In this group the test is 90% sensitive on CSF and 50% sensitive on serum. False positives mey be as high as 9.5% but these are relatively easy to prevent with pre-heating and use of proper controls (1,14,15). Complement fixation is 100% specific but only 35% sensitive.

In 1985 Jensen et al reported 3 patients with cryptococcal pneumonia who had positive sera for cryptococcal antigen and raised the possibility that this test would be useful in making the diagnosis of cryptococcal pneumonia. In other reports of cryptococcal pneumonia, four of seven were positive for cryptococcal antigen in serum (15,16,25). A larger series, however, reported only 1/14 cases of cryptococcal pneumonia as (+) for serum antigen (14). It is currently unknown if the serum cryptococcal antigen might be (+) in cases of mere colonization.

THERAPY

Since Kerkering's article it has been recommended that abnormal hosts with pulmonary cryptococcosis be treated with anti-fungal therapy while normal hosts can be observed without therapy. The therapy found by Kerkering et al to be effective in cryptococcal pulmonary disease was derived from the regimen used for meningitis: ampho B .3mg/kg/day and flucytosine 150 mg/kg/day for 6 weeks. The Mycoses Study Group had found this regimen to give a 67% rate of cure or improvement of cryptococcal meningitis compared to 41% for ampho B alone, given as .4 mg/kg/day X 7 weeks and then .8mg/kg on alternate days for 4 more weeks (31). Sabetta and Andriole (19) took exception to this and stated that earlier studies using amphotericin B alone at a dose of .6 to 1mg/kg/day for 2 or 3 months had achieved comparable results, with cure rates of 47-58%. Certainly there is no data comparing these regimens for pulmonary disease alone. A recent study stated that 4 weeks of amphotericin and flucytosine could be used in non-immunosuppressed patients with crytococcal meningitis with a high degree of success (34). In the 1983 Mycoses Study Group article on ketoconazole there were three patients with pulmonary cryptococcal disease. Two of the three improved on ketoconazole 400-600 mg per day. One author has recommended that if ketoconazole were to be used for pulmonary cryptococcosis it should be given for at least 6 months (1).

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ZYGOMYCOSIS

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GENERAL

Zygomycosis, formerly known as mucormycosis or phycomycosis, refers to human disease caused by fungi of the class Zygomycetes. Two orders of Zygomycetes produce disease: Entomophthorales and Mucorales. *Mucor*, *Rhizopus*, and *Absidia* are the genera of Mucorales which cause most zygomycotic infections (25). The organisms are worldwide in distribution and are found on bread, fruit, and in the soil.

The five forms of disease tend to occur in particular conditions. Gastrointestinal disease occurs in malnourished children, cutaneous infection in patients with burns or other dermal injury. Rhinocerebral infection occurs in ketoacidotic diabetics, while pulmonary zygomycosis occurs in leukemia and other conditions of profound immunosuppression, as does the disseminated form of disease (26). Only the last three categories will be discussed here.

The organism may be found as normal flora or as a laboratory contaminant, but a positive sputum culture in an immunocompromised host is highly suggestive of invasive disease (20,21).

RHINOCEREBRAL DISEASE

Clinical Manifestations

Diabetic ketoacidosis provides the most favorable conditions for the mucoraceae: a high glucose and an acid pH (26). Infection usually begins in the nasal sinus or palate and extends to the adjacent paranasal sinuses. It may also extend through the apex of the orbit into the brain. A black eschar may appear on the palate or nasal mucosa. Drainage of black necrotic material from the eye or nares is an additional diagnostic clue (6). Patients may complain of lethargy, headache, or visual loss (5). Physical findings may include cranial nerve palsies, proptosis, and periorbital cellulitis. Sinus films frequently show bone destruction as well as air-fluid levels. Complications include cavernous sinus thrombosis, seizures, stroke syndromes, and internal carotid artery thrombosis. Meningoencephalitis may occur with extension of the infection through the paranasal sinuses and into the cranium.

Diagnosis and Therapy

The diagnosis of rhinocerebral zygomycosis is based on biopsy specimens revealing broad non-septate hyphae invading tissue. Cultures are often positive but the clinical picture is more important for diagnosis. Blood cultures are rarely positive. CSF findings may be normal or nonspecific. Successful treatment requires control of DKA, aggressive surgical debridement, and amphotericin.

PULMONARY ZYGOMYCOSIS

Clinical Manifestations

Pulmonary involvement is almost always seen in immunocompromised hosts. Associated conditions have included renal failure, organ transplant, hematologic malignancies, agammaglobulinemia, steroid therapy, diabetes, prolonged postoperative course, chronic salicylate acidosis and rarely a normal host (21,25,26). A typical scenario would be an immunosuppressed patient at his neutropenic nadir who becomes profoundly ill with development of cough, fever, sputum production, and an infiltrate unresponsive to antibiotics. Hemoptysis may occur and may be massive.

The most typical radiographic findings are those consistent with vascular occlusion, i.e. a nodular or acinar infiltrate which develops into a wedge shaped density extending toward the pleura (21). However a wide variety of patterns have been described including asymptomatic solitary nodule, single or multiple abscess cavities, mycetoma, lobar infiltrates, miliary pattern, mediastinal widening, and pleural effusion (21,16).

There is an additional syndrome particular to diabetic patients, consisting of localized endobronchial involvement. Patients may present with hoarseness, tracheal obstruction, atelectasis from bronchial obstruction, or massive hemoptysis from invasion of hilar vessels. With aggressive surgical management, cure is possible (21,22,26).

The lungs are often the source for hematologic dissemination which may go to spleen, kidney, skin, heart, or GI tract. However, the CNS is the most common site of spread, with formation of infarcts and abscesses (7,26).

Diagnosis and Therapy

Antemortem diagnosis has been the exception rather than the rule in patients with pulmonary zygomycosis because of the acuteness of course, failure to consider the diagnosis, and necessity of an invasive procedure to establish the diagnosis. Successful procedures have included transbronchial biopsy, bronchoalveolar lavage, percutaneous needle aspiration, and open lung biopsy (21,25,26). Histologically, one finds tissue invasion by broad, non-septate hyphae with right angle branching, and a tendency toward vascular occlusion with massive hyphal growth and secondary thrombosis. It is not known why mucorales have such a predisposition to grow in and through blood vessels. Culture of histologic specimens is usually negative (25,26). There is currently no serologic assay which has demonstrated utility, (24) but the CDC has developed an enzyme immunoassay which, if found to be sufficiently accurate in clinical studies, may be available in the future (25).

Experience with therapy is limited by the infrequency of antemortem diagnosis. Successful outcome appears to depend on early diagnosis, aggressive resection of any localized disease, and amphotericin B. Even more important than these measures is control of the underlying disease which is usually the most difficult aspect of therapy. Some advocate withdrawal of immunosuppressive therapy or steroids if the lesion is not resectable (6,21,26). Hyperglycemia or acidosis should be controlled if present. Of 19 reported cases of successful therapy, 10 patients were diabetic, and two had no apparent underlying disorder. Twelve patients had localized disease amenable to surgical debridement and seven were successfully treated with amphotericin B alone.

Antifungal agents other than amphotericin have no consistent in vitro or in vivo effectiveness and there is no role for combination anti-fungal chemotherapy (6,21,26). Amphotericin dose should be individualized but may exceed 2-4 grams (15-18). If surgical resection is contemplated, amphotericin should be administered preoperatively if the diagnosis is known, or postoperatively if there is residual disease. Asymptomatic mycetomas should be resected because of the organism's propensity to vascular invasion, massive hemoptysis, and, in the immunocompromised host, to dissemination (26).

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PULMONARY DISEASE IN THE IMMUNOCOMPROMISED HOST

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The immunocompromised host (ICH) constitutes an increasingly significant problem to clinicians for several reasons: (1) there is increased reliance on organ transplantation; (2) there are a growing number of indications for the use of antineoplastic agents to treat malignancies; (3) there is more aggressive use of corticosteroids and other immunosuppressives to treat non-malignant diseases; and (4) a new disease, the acquired immune deficiency syndrome (AIDS), has emerged. Furthermore, we now have more effective therapy to treat pulmonary complications in the ICH, offering a greater challenge to make the correct diagnosis.

This chapter will summarize some of the clinical features of lung disease in the ICH and review logical steps toward diagnosis. No attempt will be made to review specific therapy. Much of the organization of this chapter was inspired by an excellent monograph (unpublished, 1980) by Dr. E.C. Rosenow III of the Mayo Clinic. The best recent review of infectious agents will be found in reference 1.

The immunocompromised host is one whose defense mechanisms to infection are impaired. The following is a list of the diseases most frequently encountered in clinical practice which result in an immunocompromised state. The disease states identified by asterisks are the ones most likely to present with pulmonary complications.

*Cancer
*Hodgkin's disease
*Non-Hodgkin's lymphoma
*Leukemia
*Agranulocytosis, primary and secondary
Burns
Childhood granulomatous disease
Cirrhosis
Connective tissue disorders
Diabetes mellitus (poorly controlled)
Immunoglobulin deficiencies (B cell disorders)
    a. inherited
    *b. acquired
Sarcoidosis
Sickle cell anemia
T cell disorders
    a. inherited
    *b. acquired (this includes AIDS patients)

ETIOLOGY OF PULMONARY INFILTRATES IN THE IMMUNOCOMPROMISED HOST

There are four causes for new pulmonary disease in the ICH.

I. Extension of the underlying disease process -- The most frequent diseases associated with immunocompromised patients that can histologically and radiographically involve the lung are:

a. Leukemia - Pulmonary infiltrates in the patient with leukemia are far more likely to be due to infection (or something else) than to leukemic infiltration (2,3). Infiltration is four times more likely to be found histologically (usually at autopsy) than clinically or radiographically (4). Pulmonary infiltrates due to leukemia are diffuse and interstitial, although there may be an alveolar component when acute. Occasionally the infiltrate may be localized. Infiltrates almost never occur when the leukemia is in remission. Leukemic infiltrations are most common with AMML and CLL, particularly in the terminal phase. Mediastinal adenopathy is found in 25%, and pleural effusion is also found in 25% but is rarely due to actual pleural involvement by leukemic cells. Leukostatic thrombi of the pulmonary vessels may occur when the WBC count is greater than 200,000 and is usually associated with blastic degeneration. A large consolidation may be due to hemorrhage. Patients with acute untreated leukemia are usually only susceptible to infection as a result of neutropenia or hypogammaglobulinemia; their humoral and cell-mediated immune systems remain intact until cytotoxic therapy is begun. In CML, most patients have impairment of phagocytosis, and some have T-cell defects as well, but infection is not a significant problem until blast crisis ensues (blast cells are ineffective phagocytes).

b. Lymphoma - With rare exceptions, the presenting feature of untreated lymphoma is not infection. Thus, a pulmonary parenchymal abnormality in the patient with untreated lymphoma is most frequently the lymphoma itself; opportunistic infection tends to occur only after treatment. Lung involvement is much more common in Hodgkin's disease, especially nodular sclerosing Hodgkin's disease, than in non-Hodgkin's lymphoma. The initial radiographic manifestations of lung involvement by lymphoma can be classified into four categories: (1) homogeneous confluent infiltrates which may cavitate; (2) fibronodular infiltrates; (3) discrete nodules; and (4) true consolidation (may have air bronchograms). Lymphoma in the lung almost never presents with acute pulmonary symptoms, but it can mimic subacute pulmonary processes such as nocardiosis, tuberculosis, cryptococcosis, invasive aspergillosis and, rarely, pneumocystosis. The patient with parenchymal Hodgkin's disease almost always has associated mediastinal and/or hilar adenopathy, unless prior radiation of the mediastinum was given. This is not true with non-Hodgkin's lymphoma, which may have significant parenchymal change without adenopathy. Adenopathy very rarely occurs with opportunistic infection.

c. Carcinoma and Sarcoma - Metastatic lymphangitic spread of carcinoma usually presents clinically as a subacute to chronic process, progressing over at least several weeks' time. The presence of Kerley-B lines may be a significant clue; these will not disappear with diuresis. Adenocarcinoma is by far the most common type of tumor to present with lymphangitic metastasis. Sarcomas rarely do; instead they present as discrete cannonballs, and are rarely confused with any other condition. Induced sputums for cytologic examination are positive in over 50% of lymphangitic carcinomas, and transbronchoscopic lung biopsy is even more rewarding (5). Patients with carcinoma or sarcoma requiring chemotherapy are predisposed to developing a second primary neoplasm.

d. Organ Transplant Complications - The kidney is the most common solid organ transplanted, followed by bone marrow, heart, and liver in that order. Each organ transplanted presents its own peculiar set of complications, such as the graft-versus-host-reaction seen in bone marrow transplants. Since renal transplantation is the most common transplantation performed, discussion will be limited to that organ. Opportunistic infection will be covered in detail later but it is one of the major causes of death in this group of patients (6). The phenomenon of rejection crisis pulmonary edema is due to hypervolemia caused by renal insufficiency. Steroids are effective in this disorder because they reduce rejection phenomena and improve renal function. Several reports have shown an increased incidence of neoplasia, including lung cancer, in patients with chronic renal failure, unrelated to chemical immunosuppression. Chronic renal failure results in a T-cell type of deficiency and lack of immuno-surveillance is postulated as the cause for the increased risk. Similar incidences have been reported in renal transplant patients.

e. Connective Tissue Disorders - Most connective tissue diseases have associated pulmonary abnormalities, but their presentation is usually characteristic enough that roentgenographic diagnosis is not too difficult if pulmonary manifestations occur in the presence of typical systemic or serologic manifestations (7). The problem arises when pulmonary disease occurs while the patient is being treated with anti-inflammatory and immunosuppressive drugs. The differential then is between the basic disease, drug reaction, and infection. With very few exceptions, the onset of the pulmonary component of the basic disease is insidious. However, pulmonary vasculitis can occur acutely, as can acute lupus pneumonitis. Moreover the connective tissue diseases are associated with T-cell disorders when very active or far advanced, resulting in an immunocompromised state with increased risk of both opportunistic and non-opportunistic infection.

II. Opportunistic Infection -- The lung is the most frequent documented site of infection in patients with cancer; pneumonia accounts for up to 50% of infectious deaths in patients with hematologic malignancy (8). Because pulmonary infection in the ICH can be rapidly fatal, new infiltrates should be considered infections until proven otherwise.

Patients with AIDS are especially prone to opportunistic pulmonary infection with *Pneumocystis carinii*, *Cryptococcus*, and cytomegalovirus. Less frequently, atypical mycobacteria, *Aspergillus*, and *Nocardia* are seen in this group. It is not uncommon for more than one infectious process to be present at the same time (9).

The term "opportunistic" is generally understood to mean infection by organisms that are ordinarily non-pathogenic in normal hosts, who may regularly encounter or carry such organisms. Only when the opportunity is provided by disease- or drug-induced alteration of host defense mechanisms do such normally harmless organisms invade the host and produce overt disease. In addition to being prey to opportunistic organisms, compromised hosts are also attacked by common pathogens. The lung is the site of the most troublesome infections occurring in immunocompromised hosts. An obscure pulmonary infiltrate associated with fever represents a common diagnostic problem. The type of underlying defect in host defenses makes certain pulmonary infections more likely (Table 1).

The presence of fever and an abnormal chest radiograph in an immunosuppressed patient makes consideration of infection mandatory. The approach to the differential diagnosis must be both systematic and thorough due to the many causes of pulmonary infection and the specificity and potential toxicity of their respective treatments. The manifestations of infection in the ICH may be altered by the underlying conditions of the host and may therefore be subtle. For example, the sputum of patients with bacterial pneumonia and severe granulocytopenia may not be as purulent as expected because the host cannot mobilize sufficient polymorphonuclear leukocytes to generate purulence. Also, the chest x-ray may not become abnormal until a day or more after symptoms first occur. The approach to diagnosis depends upon three factors: the pace and severity of the illness, the underlying disease, and the availability of medical and surgical personnel.

III. Pulmonary Reaction to Drugs - Some chemotherapeutic agents are well known to induce pulmonary disease, while with others the association is weaker. Some agents, on the other hand, have never been associated with pulmonary toxicity. (Table 2) (9,10)

Drugs may cause pulmonary disease via either non-cytotoxic or cytotoxic reactions. The non-cytotoxic reactions are usually acute syndromes occurring early in the treatment course, frequently associated with eosinophilia and/or fever, and usually reversible with withdrawal of the drug with or without the addition of steroids. Cellular atypia of alveolar lining cells is not present. The prototypical example of the non-cytotoxic reaction is methotrexate-induced pneumonitis, which appears 10 days to four months after the beginning of methotrexate therapy. The patients present with dry cough, dyspnea and fever; over half will have eosinophilia. Open lung biopsy shows non-specific histology. The chest x-ray will show a diffuse interstitial and/or alveolar pattern with hilar adenopathy in 10% and pleural effusion in 10%. Patients recover completely upon stopping the drug and adding steroids. Interestingly, they usually will have no recurrence with a rechallenge.

Cytotoxic reactions, on the other hand, usually occur later in the course of treatment and have a more subacute or chronic course. There is no associated eosinophilia. Fever may or may not be present. Lung biopsy (or even sputum, in some instances) shows marked cellular atypia, especially of the type II pneumocyte, which is virtually diagnostic. Cytotoxic drug reactions are frequently irreversible and may relentlessly progress to death. The prototypical drug in this category is busulfan. Bleomycin has been associated with a few cases of an acute hypersensitivity-type reaction with eosinophilia, but is much more frequently associated with a subacute cytotoxic reaction similar to busulfan. Prior or concomitant radiation therapy involving the lungs predisposes to adverse drug effects.

Corticosteroids do not in themselves cause any known lung disease. Their immunosuppressive effect does, however, predispose to certain opportunistic infections, especially Pneumocystis carinii pneumonia, CMV pneumonia, nocardiosis, and aspergillosis. Reactivation of tuberculosis in the patient on steroids is well described, although this does not occur with the equivalent of 15 mgs or less of prednisone per day. Mediastinal lipomatosis (a result of the alteration of lipid metabolism induced by steroids) can also occur and creates a confusing chest x-ray which is suggestive of a mediastinal mass. CT of the mediastinum, however, shows characteristic fat deposition.

Radiation therapy (a drug of sorts) is well known to cause pulmonary disease in two phases (11). Radiation pneumonitis usually has a subacute presentation, and may begin two to six months after x-ray therapy is completed. (Rule: expect radiation changes 8 weeks after 4,000 rads and 1 week earlier for each 1,000 rad increase over 4,000 rads.) Patients present with nonproductive cough, dyspnea, fever and a sensation of fullness in the chest. Hemoptysis and chest pain are rare. The chest x-ray typically shows a spectrum from diffuse haziness or indistinctness in pulmonary markings to frank alveolar consolidation, with sharp edges corresponding to the margins of the port. There have been several reports of radiation pneumonitis extending outside the margins of the port, or even in the contralateral lung, but this is distinctly unusual. Patients usually respond to high dose steroids begun immediately at the onset of symptoms. Radiation fibrosis occurs later, and is usually a gradual evolution of the earlier radiation pneumonitis. The changes usually evolve slowly from pneumonitis to fibrosis over six months or more, and will stabilize at 10 to 12 months after x-ray therapy is completed. The chest x-ray at that time will show parenchymal retraction, pleural thickening, an elevated diaphragm, and bronchiectasis or cystic areas in the region of the port. Steroids are of no benefit at this stage; although the earlier radiation pneumonitis does respond to steroids, it is not clear whether such therapy affects the subsequent development of fibrosis. The disability produced is dependent upon several factors: (1) pulmonary function prior to radiation, (2) amount of lung radiated, (3) radiation dose, (4) concomitant drug therapy, (5) history of prior radiation therapy and (6) underlying disease. Most patients receiving radiotherapy to the lungs will have x-ray changes following treatment; only about 10% will have symptoms and very few (fewer than 1%) will die. Radiation-induced lung damage is most significant in patients with marginal pulmonary reserve prior to treatment.

IV. *New, Unrelated Pulmonary Disease Process* -- A confusing array of pulmonary conditions can occur in the ICH as a result of underlying debility, diagnostic tests performed, or therapeutic measures used. The following is a partial listing:

a. *The adult respiratory distress syndrome (ARDS)* has been associated with a number of precipitating factors, including shock, gram negative sepsis, and blood transfusion.

b. *Left heart failure* should be kept in mind in the elderly patient, and in those receiving doxorubicin or daunorubicin anthracycline antibiotics, which show a dose-related cardiotoxicity. Left ventricular failure in the ICH usually has an insidious onset. An elevated wedge pressure is diagnostic, but clinical suspicion and response to a trial of diuresis may secure the diagnosis without invasive procedures.

c. Pulmonary emboli can occur even in the setting of platelet counts below 20,000 and diagnosis is notoriously difficult. If there is any underlying pulmonary disease, an abnormal scan will probably be uninterpretable; it will only be diagnostic if normal. Pulmonary angiography is usually required for diagnosis.

d. Aspiration pneumonia can present as ARDS, or as focal or diffuse infiltrates, and is common in the debilitated patient or one with a nasogastric tube.

e. Oxygen toxicity is likely in the patient maintained on FiO_2 greater than 80% for more than 48 hours; the risk is greater with certain types of chemotherapy, such as bleomycin. However, it takes 5 to 10 days to cause the radiographic changes of ARDS oxygen toxicity, and thus infrequently is part of the differential in the acute pulmonary decompensation of the immunocompromised patient.

f. Neoplasm such as bronchogenic carcinoma and non-Hodgkin's lymphoma are found in increased frequency in immunosuppressed patients.

g. ICH patients are as eligible to get a non-opportunistic pneumonia (such as mycoplasma or viral) as the next person but the infection may be more severe. There is probably an increased incidence of common infections in immunocompromised patients but there are no available statistics.

h. Leukoagglutinin transfusion reaction is a transient noncardiac pulmonary edema secondary to antibodies to leukocytes in donor's blood. The chest x-ray shows bilateral interstitial infiltrates but clears within 24 hours. This syndrome is probably more common than recognized.

i. Hemorrhagic lung tends to be a "related" condition because of the common findings of thrombocytopenia and other clotting disorders in these patients, but pulmonary hemorrhage is uncommon unless an invasive procedure such as transbronchial lung biopsy or transthoracic needle aspiration is attempted. It may not appear on the immediate post-procedure CXR, only to develop the next day as a "new" process. Patients usually have blood in the sputum, which may aid diagnosis.

j. Lymphangiogram contrast emboli can be fatal. Predisposing factors include the presence of COPD, mediastinal disease, and infusion of too much contrast too rapidly. The disorder usually presents immediately upon infusion but can occasionally present clinically several days later.

CAVEATS IN THE DIAGNOSIS OF PULMONARY DISEASE IN THE IMMUNOCOMPROMISED HOST

1. Hesitation in performing diagnostic procedures, while the patient steadily deteriorates to the point when invasive diagnostic procedures can no longer be considered, may increase morbidity and mortality.

2. Even after autopsy, fatal pulmonary disease in the ICH remains undiagnosed in 15% of patients.

3. The clinical diagnosis regarding the cause of the infiltrate is wrong over 50% of the time (12,13).

4. Fever in the ICH has a 75% chance of being related to infection (95% in acute myelomonocytic leukemia) (4). Absence of fever does not mean absence of infection, however.

5. Serum should be stored in all ICH patients; it may be valuable later in documenting seroconversion with respect to certain infections.

6. In the febrile ICH patient with undiagnosed fever and negative chest x-ray, the chest x-ray should be repeated at appropriate intervals, as new infiltrates may appear.

7. The exact etiology of pulmonary disease in the ICH cannot be predicted by the chest x-ray appearance.

8. The acute leukemias rarely present with pulmonary disease until they are treated, are neutropenic, or have a high percentage of blasts in the peripheral blood (3).

9. Almost all the *common* bacterial pneumonias in the ICH have positive blood cultures, but sputum cultures are positive in fewer than 20% (14). Neutropenic infections begin when the absolute PMN count reaches less than 1000. If neutropenia is present for greater than 12 weeks, over 90% will become infected.

10. It is uncommon to have disseminated candida infection in the immunocompromised host unless that patient has been on long term antibiotics, is severely neutropenic, or has a break in the mucosal barrier (e.g. hyperalimentation line) (15).

11. *Pneumocystis carinii* pneumonia is very uncommon unless the patient hasbeen on high dose corticosteroids and/or cyclophosphamide, or has AIDS.

12. Legionnaire's disease should be suspected in the patient with diarrhea, hyponatremia, hypophosphatemia, bradycardia or mental status changes.

13. Anaerobic pulmonary infections are very uncommon in the ICH.

14. Herpes simplex and varicella-zoster pneumonia should have associated skin lesions.

15. Radiation pneumonitis can involve lung tissue outside the port of treatment and radiologically and histologically mimic cytotoxic lung (11).

16. CMV pneumonitis most often is found in association with other infections, especially Pneumocystis.

17. The presence of aspergillus in the nasal culture points to the possibility of invasive pulmonary aspergillosis in the ICH. Invasive aspergillus infection rarely occurs in the absence of neutropenia and is found most commonly in leukemia or lymphoma.

18. If neutropenia is present, the patient is much more likely to have a negative chest x-ray early in the course of gram negative bacillary pneumonia.

19. In the splenectomized patient infection with encapsulated bacteria, i.e. Streptococcus pneumoniae, Hemophilus influenzae, and Neisseria should be considered.

20. The patient with Hodgkin's disease is especially prone to cryptococcal and disseminated varicella-zoster infection.

21. The patient with perianal or perirectal infection will frequently have Pseudomonas bacteremia.

22. In the patient with acute (minutes to hours) evolution of hypoxemia, Pneumocystis carinii infection, pulmonary edema, pulmonary embolus, and aspiration pneumonia should come to mind.

23. The patient with end-stage liver disease is prone to gram negative infections.

24. The AIDS patient is most prone to Pneumocystis carinii pneumonia.

DIAGNOSTIC TECHNIQUES IN THE EVALUATION OF PULMONARY DISEASE IN THE IMMUNOCOMPROMISED HOST

Unfortunately, there is no "cookbook" algorithm on how to approach the ICH patient with pulmonary disease. However, if one is familiar with the underlying disease process and its associated immunodeficiencies, and with the factors that predispose that patient to complications of his disease, one can come up with a reasonable differential diagnosis and proceed accordingly. It should be remembered that it is not at all uncommon to have two or more separate pulmonary conditions, such as infection and drug reaction, in the same patient.

Eventually with each patient one will have to decide how aggressive to be, which usually depends on the severity and the rapidity of the process. On one extreme, an open lung biopsy could be performed on every patient; on the other extreme one could empirically treat for the most likely cause(s). In the neutropenic febrile patient with an abnormal chest x-ray, after appropriate blood and other cultures have been taken, a trial of two or three broad spectrum antibiotics is justified for a few days (e.g. piperacillin and gentamicin) before proceeding to the more invasive procedures. A point that must be strongly emphasized is to not wait too long before considering an invasive procedure. Hesitation may allow for deterioration to occur to the point that the patient is too sick for an invasive procedure.

If after 48 hours of empiric treatment the patient's condition has not improved (or is worsening), and if the diagnosis has not yet been established, an important clinical decision must be made. The clinician must choose between an invasive procedure to further investigate the patient's illness, or broadening the empiric coverage to include other possible infectious agents. For instance this might involve adding trimethoprim-sulfamethoxazole (for *Pneumocystis*), erythromycin (for *Legionella*), amphotericin B and/or antituberculous therapy to the already present combination of piperacillin and gentamicin.

There are several procedures available to diagnose pulmonary disease in the ICH. Not all of these are useful; some have fallen out of style.

1. *Noninvasively obtained secretions* for staining, culture, and cytology including sputum (spontaneous or induced), blood, and nasal smears are occasionally useful. Sufficient sputum production for examination is not available in many patients, as the neutropenic patient is unable to muster enough cells to form purulent material. Some series report less than 20% positive sputum cultures in patients with bacterial pneumonias (14), but the blood cultures are usually positive. Two noninfectious conditions that may be diagnosed with sputum studies are cytotoxic drug-induced pulmonary disease and carcinoma. Experienced cytopathologists can recognize the typical changes of cytotoxic drug effects on the Type II alveolar pneumocyte (10).

2. *Transtracheal aspiration (TTA)* fluctuates in popularity. The yield of this procedure is not very good in the

patient with a nonproductive cough. The most serious complication of TTA is bleeding, which may be very difficult to control. This procedure should not be employed in the patient who is uncooperative, or who has an abnormal PT/PTT, a platelet count of less than 100,000, or a PaO_2 less than 70 torr on supplemental oxygen. *Pneumocystis* is almost never diagnosed by this technique.

3. *Transthoracic needle aspiration* should probably be considered more often than it is when infection is strongly suspected; however, pneumothorax is common and fatal hemorrhage can occur. Transthoracic needle biopsy and percutaneous trephine drill biopsy obtain excellent pieces of tissue, but these techniques are rarely used now due to their unacceptable risks (pneumothorax is almost routine) (13).

4. *Fiberoptic bronchoscopy* (15,16) is a relatively riskless procedure in good hands and can be done in seriously ill patients even at the bedside. Using the sterile sheathed catheter to obtain material for culture through the fiberoptic bronchoscope may arguably improve the yield in this procedure, but the supporting laboratory must be experienced in performing quantitative cultures; moreover, prior antibiotic therapy invalidates the results. Transbronchoscopic lung biopsy has a high yield (75%), at least for *Pneumocystis*, and should be done when suspicion for this organism is great. Invasive fungal disease and CMV, however, are rarely diagnosed by bronchoscopy. Complications of fiberoptic bronchoscopy with transbronchoscopic biopsy include bleeding and pneumothorax, with bleeding the more serious, but both are rare. This procedure should not be undertaken with a platelet count of less than 50,000 or in the presence of uremia (which causes a qualitative platelet defect).

5. *Open lung biopsy* is the "gold standard" diagnostic procedure against which other procedures must be compared. However, it must be remembered that even with this procedure, the diagnosis of pulmonary infiltrates in the immunocompromised host will remain obscure in over 15%.

Usually, the final choice is between fiberoptic bronchoscopy with transbronchoscopic biopsy and open lung biopsy. Review of the literature discloses conflicting information in comparing the yield of the two procedures. There is no report in which a series of patients first had bronchoscopy and then immediately went to open lung biopsy, with a comparison of results. Fewer options are available to the pathologist for processing specimens obtained by transbronchoscopic lung biopsy, since the physical size of the specimen obtained is a limiting factor. There is usually insufficient material available to perform frozen sections or touch preps for *Pneumocystis*, so results may be unavailable for 24-48 hours. (Specimens can be processed in about 8 hours by a well-equipped pathology lab, although this is a labor-intensive proposition.) Since open lung biopsy specimens are much larger, they can be processed within hours, and this may be particularly important in the rapidly deteriorating patient. In the setting where bleeding difficulties may be anticipated, the open lung biopsy with direct visualization and control of bleeding vessels is clearly the procedure of choice. The open lung biopsy can be performed on extremely ill patients, including those on ventilators with PEEP (12). Deaths as a result of the procedure are extremely rare; the only significant complication is an air leak requiring prolonged chest tube drainage.

CONCLUSION

The clinician must be aggressive in the diagnostic workup of pulmonary disease in the ICH. If after the first 48 hours of empiric therapy, the patient's condition has not improved or has worsened, an invasive procedure should be seriously considered. Fiberoptic bronchoscopy with transbronchoscopic lung biopsy is probably the correct choice if one can afford to wait for the result, and still have time for an open lung biopsy if the bronchoscopy is non-diagnostic. If the patient is rapidly deteriorating, open lung biopsy would be the first procedure of choice.

TABLE 1

PULMONARY PATHOGENS IN PATIENTS WITH DEFECTS IN HOST DEFENSES

Impairment	Usual Pathogens
1. Impaired granulocyte function (myelocytic leukemia, uremia, polycythemia vera, burns, corticosteroid therapy, drug-induced granulocytopenia)	Enterobacteriaceae *Pseudomonas aeruginosa* *Staphylococcus aureus* *Nocardia asteroides* *Candida* spp. *Aspergillus* spp.
2. B cell disease-impaired antibody formation (lymphocytic leukemia, multiple myeloma, histiocytic lymphoma, nephrotic syndrome, corticosteroid therapy, alkylating agents)	*Streptococcus pneumoniae* *Pseudomonas aeruginosa* *Hemophilus influenzae* *Pneumocystis carinii*
3. T cell disease-anergy (Lymphomas, terminal cancer, uremia, corticosteroid therapy, sarcoidosis, alkylating agents, antimetabolites)	*Cryptococcus neoformans* *Mycobacterium tuberculosis* Viruses *Pneumocystis carinii* *Toxoplasma gondii* *Candida* spp. *Nocardia asteroides*

TABLE 2

CHEMOTHERAPEUTIC AGENTS INDUCING PULMONARY DISEASE

1. Cytotoxic
    - Busulfan
    - Cyclophosphamide
    - Bleomycin
    - Nitrosoureas (BCNU, CCNU, methyl-CCNU)
    - Chlorambucil
    - Mitomycin C
    - Hydroxyurea
2. Non-cytotoxic
    - Methotrexate
    - Procarbazine
    - Bleomycin
3. No known pulmonary disease associated
    - Fluorouracil
    - Vinca alkaloids (vincristine, vinblastine)
    - Cytarabine
    - Doxorubicin
    - Thiotepa
    - Azathioprine
    - Corticosteroids

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PULMONARY COMPLICATIONS OF AIDS

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Infection with the human immunodeficiency virus (HIV) has reached epidemic proportions. A cohort analysis of 6000 homosexual males begun in 1978 and completed in 1986 demonstrated HIV seroconversion in 70% of the cohort. In a subgroup who were seropositive at the start of the study, 15% subsequently developed AIDS, and 51% developed AIDS-related complex (ARC), while only 39% were asymptomatic at six years follow-up. In 1991 an estimated 270,000 AIDS cases will have been diagnosed, an estimated 179,000 deaths will have resulted from AIDS, and 74,000 new cases will be diagnosed that year (1). Since 40 to 50% of these patients will develop pulmonary complications, the AIDS epidemic will have a major impact on pulmonologists (2-3).

The pulmonary complications of AIDS are conveniently classified as: 1) opportunistic infections diagnostic of AIDS, 2) HIV-related pulmonary infections, 3) presumed HIV-related pulmonary disorders, and 4) AIDS-related pulmonary neoplasia. For this discussion, Pneumocystis carinii pneumonia (PCP), Mycobacterium avium complex disease (MAC), and cytomegalovirus (CMV) pneumonia will be examined as the most common examples of opportunistic infections diagnostic of AIDS. Pulmonary fungal infections and tuberculosis will be studied as HIV-related pulmonary infections. Pyogenic bacterial pneumonia is increasingly recognized as an HIV-related disorder. Finally, pulmonary Kaposi's sarcoma provides an example of AIDS-related neoplasia. It should be noted that the majority of pulmonary complications are infectious. A complete list of pulmonary complications of AIDS is found in the appendix.

DIAGNOSTIC APPROACH

The diagnosis of AIDS-related pulmonary disease begins with the history and physical exam. The appropriate risk factors for HIV infection, homosexuality, heterosexual contact with an HIV positive partner, IV drug abuse, hemophilia, or receipt of blood transfusions prior to 1985 are usually present. Physical exam may reveal oral candidiasis, hairy leukoplakia, cutaneous Kaposi's sarcoma, or diffuse lymphadenopathy. Symptoms and findings related to the pulmonary system are non-specific and include dyspnea, cough, stridor, wheezing, tachypnea, fever, and rales. Given the non-specificity of these findings further evaluation is needed in AIDS patients with pulmonary symptoms.

The chest radiograph offers little help in the differential diagnosis of pulmonary complications in AIDS patients. From 10 to 20% of patients with PCP, MAC, and CMV pneumonia may have a normal chest x-ray on presentation (3-5). The majority of patients present with diffuse infiltrates on chest x-ray. Lobar consolidation strongly suggests bacterial pneumonia, though it has been reported with PCP (4-5). Other clues may suggest a specific pulmonary complication, but there are no diagnostic radiographic patterns. Details of the radiography of specific pulmonary complications may be found in the appropriate sections below.

Sputum examination should be done in all AIDS patients and may be helpful in the diagnosis of PCP, MAC, tuberculosis and fungal diseases. Sputum examination is not useful for the diagnosis of CMV disease or pulmonary Kaposi's (3,6-8). Sputum examination should include silver or Giemsa stains for PCP, as well as acid-fast and fungal smears and cultures. Often sputum examination will not provide a diagnosis, and invasive tests are required.

Fiberoptic bronchoscopy will establish the diagnosis of an opportunistic pulmonary infection in 96% of patients (9). The yield is lowest for MAC and highest for PCP (2). The combined use of transbronchial biopsy and bronchoalveolar lavage results in a higher yield for all pathogens (except cryptococcus) than either procedure alone (9-10). Bronchoscopy is of limited value in making a diagnosis of pulmonary Kaposi's sarcoma. Transbronchial biopsies are usually negative, but bronchoscopy may allow visualization of endobronchial Kaposi's (3, 11-12). The key point is that bronchoscopy is very reliable in diagnosing treatable pulmonary disease in AIDS patients. Recently, techniques for non-bronchoscopic lung lavage have been developed and have shown promising results (13).

In an AIDS patient with pulmonary symptoms and a negative bronchoscopy , additional diagnostic procedures may be required. A clinically stable patient may simply be observed. A clinically unstable patient should probably undergo repeat bronchoscopy or open lung biopsy. However, the yield of open lung biopsy for opportunistic infections in AIDS is comparable to bronchoscopy, and usually will not show a treatable pathogen with a negative antecedent bronchoscopy (14). Barrio and colleagues recently evaluated the yield of repeat bronchoscopy in AIDS. In patients with clinical deterioration shortly following either a diagnostic or non-diagnostic initial bronchoscopy, a treatable condition was found on repeat bronchoscopy in only 5%. This group had a 62% mortality. In patients who developed new pulmonary infiltrates after successful treatment of an opportunistic infection, a treatable condition was noted on repeat bronchoscopy in 59%. This group's mortality was 30% (15). In summary, repeat bronchoscopy or open lung biopsy is unlikely to diagnose a treatable condition if the initial bronchoscopy is negative.

PNEUMOCYSTIS CARINII PNEUMONIA

Pneumocystis carinii pneumonia (PCP) is the most common pulmonary complication of AIDS. It has been reported in 46 to 85% of patients with pulmonary complications (2-4,8). Symptoms of fever, dyspnea and cough are common occurring in 60 to 85% of patients. In contrast to the leukemic population, the median duration of symptoms in AIDS patients is 3 to 4 weeks. Pulmonary auscultatory findings are noted in only 50% of patients (16). On pulmonary function testing AIDS patients with PCP show restrictive physiology. The mean vital capacity is 53% of predicted. Obstruction is not evident, the mean FEV_1/FVC averaging 84%. The mean DLCO is 55% of predicted. The mean A-aDO2 is 47mmHg, although the PaO_2 is generally greater than 50mmHg (2, 17).

Radiographically, three common patterns are seen. An interstitial pattern, alveolar pattern, and combination interstitial-alveolar pattern are noted in 75%, 12.5% and 12.5% respectively. In addition, thin-walled cysts and honeycomb pattern are seen in up to 5%. These infiltrates are usually bilateral and distributed both centrally and peripherally in most patients (18). Rare presentations including solitary nodule and lobar infiltrates have been described in PCP (4,19). On radiographic follow-up approximately half of the patients will show radiographic deterioration at 1 week, and a third will show no change. Only 17% of patients will show radiographic regression of infiltrates at 1 week. Long term, only 43% of patients with PCP will show complete radiographic resolution (18). The chest radiograph is therefore an unreliable measure of response to therapy for PCP.

Gallium scanning for PCP in AIDS has a sensitivity of 95%, a specificity of 50%, and importantly a negative predictive value of 91% (20). A positive gallium scan must be followed by sputum examination or bronchoscopy to confirm PCP, as any infectious process will result in a positive scan. The greatest utility of gallium is in the evaluation of AIDS patients with pulmonary symptoms and a normal chest radiograph. Such patients usually require further invasive evaluation.

The diagnosis of PCP rests with the demonstration of the cyst or trophozoite form of pneumocystis in respiratory secretions, bronchial lavage or on transbronchial biopsy. Induced sputum for pneumocystis will be positive in 55% of patients when properly collected and carefully examined (8). The technique is probably not reliable in smaller medical centers without adequate technical and cytological support. Bronchoscopy with bronchoalveolar lavage alone has an 89% yield for PCP; when a transbronchial biopsy is also performed the yield increases to 95% (9). Open lung biopsy is indicated in patients with a coagulopathy and a negative lavage, and probably in patients with progressive disease and a negative transbronchial biopsy. The yield of open lung biopsy is 97%.

Standard therapy for PCP in AIDS is either trimethoprim-sulfamethoxazole (TMP/SMX) 20 mg/kg/d in three divided doses or pentamidine 4 mg/kg/d as a single I.V. dose. TMP/SMX is the recommended first-line drug based on data from non-AIDS patients. Historically, TMP/SMX had fewer adverse effects than pentamidine, and greater efficacy (17,21). However, in the AIDS population, adverse effects occur in 50% of patients given either TMP/SMX or pentamidine as initial therapy, with ultimate cures in 82 to 95% of patients (21-22). The most common adverse effects seen with TMP/SMX are rash (including Stevens-Johnson syndrome), fever and leukopenia. Pentamidine commonly causes hepatitis, azotemia, hypoglycemia and sterile abscesses. However, TMP/SMX toxicity appears to be more severe (21). Patients who require a change in therapy secondary to drug toxicity have an excellent survival, however, patients who are switched from TMP/SMX secondary to treatment failure have an 89% mortality (2).

Given an equal frequency of toxic reactions and equal treatment results from non-randomized studies, the choice of TMP/SMX as first-line therapy for PCP in AIDS may be questioned. Wharton and colleagues conducted a randomized trial of TMP/SMX versus pentamidine for therapy of PCP in AIDS (23). 41 patients were randomized to receive either TMP/SMX or pentamidine as initial therapy. Adverse reactions occurred in 41% and 44% of patients respectively. The TMP/SMX group had a 25% mortality while the pentamidine group had a 5% mortality. This difference was not statistically significant. The authors conclude that the drugs are of equal efficacy. While not statistically significant, the 25% mortality seen in the TMP/SMX group may well be clinically significant, and likely would be a statistically significant difference if the sample size were larger. Results of a second series of 70 patients randomized to TMP/SMX or pentamidine have recently been published (40). TMP/SMX patients had a significantly increased incidence of rash (15/36) and leukopenia (26/36). Pentamidine treated patients had a significantly increased incidence of hypotension (9/33), thrombocytopenia (6/33), nephrotoxicity (22/33), and hypoglycemia (7/33). Survival was greater in the TMP/SMX group (86%) than in the pentamidine group (61%). The available data seems to favor the use of TMP/SMX, but further study and newer agents are needed.

A cogent argument can be made for individualizing therapy for PCP in AIDS. TMP/SMX might be chosen as initial therapy in patients with liver disease, mild renal insufficiency, or patients with coagulopathy in whom thrombocytopenia would pose an added risk. Pentamidine might be chosen in patients requiring fluid restriction, those with pre-existent leukopenia, or prior allergy or reactions to TMP/SMX. Recently, aerosolized pentamidine has been used in a pilot study to treat PCP in AIDS with promising results and without toxicity (22). A prospective trial of aerosolized pentamidine is currently under way.

With the burgeoning population of AIDS patients effective oral therapy for PCP would offer many advantages. A pilot study of oral dapsone and trimethoprim showed an 86% cure rate without a change in therapy, and all patients ultimately survived. Adverse reactions occurred in 14/15 patients, with only 2 requiring a change in therapy, and all patients ultimately survived. Adverse reactions occurred in 14/15 patients, with only 2 requiring a change in therapy (24). Results of a prospective trial of dapsone/TMP as compared with TMP/SMX in mild PCP has been reported in abstract form. Both agents were equally effective, but the TMP/SMX group experienced greater toxicity (41).

Only two drugs have been studied as salvage therapy in patients who have failed conventional treatment for PCP in AIDS. Difluoromethylornithine (DFMO, Eflornithine) therapy resulted in a 37% survival for mechanically ventilated patients, and 76% survival for spontaneously breathing patients receiving 14 days or greater of therapy (25). Trimetrexate with leucovorin rescue in a pilot study resulted in a 69% response and survival rate as salvage therapy. As initial therapy its response and survival rates were comparable to standard therapy (26).

Corticosteroids have been evaluated in an uncontrolled fashion as adjunctive therapy for patients with PCP and acute respiratory failure. The initial results show improved survival in the steroid treated group (27-28). Further studies are underway.

Recurrent PCP occurs in approximately 25% of AIDS patients (2). To date preliminary data is available for the use of biweekly aerosolized and bimonthly intravenous pentamidine. Both agents appear promising (42-43).

MYCOBACTERIUM AVIUM COMPLEX (MAC)

Mycobacterium avium complex disease involves the lung in up to 21% of AIDS patients (2-3). It is usually disseminated at the time of diagnosis. The lung, bone marrow, liver, spleen, lymphatics and gastrointestinal tract are common sites of dissemination. MAC bacteremia is common in AIDS patients and reflects the high tissue load of organisms (29-30). Culture sites for diagnosing MAC in AIDS should include respiratory secretions, blood, stool, and urine. Bone marrow and liver biopsies may be appropriate in selected cases. Use of a Bactec system for MAC in conjunction with standard mycobacterial media has a 94% yield in recovering MA (7). The yield of bronchoscopy is 78% for MAC (2).

An analysis of therapy for MAC in AIDS is hampered by a lack of controlled data. The Center for Disease Control recommends multi-agent therapy with either a combination of ansamycin, clofazimine, isoniazid and ethambutol, or isoniazid, rifampin, and ethambutol or pyrazinamide (31). Ansamycin and clofazimine have in vitro activity against MAC but have not been shown to eradicate the organism in clinical studies (30). Therapeutic failure is likely secondary to the extremely high load of organisms in AIDS patients.

CYTOMEGALOVIRUS (CMV)

CMV pneumonia occurs in 17 to 43% of AIDS patients with pulmonary complications, and commonly occurs in association with PCP (2-3,9). Concurrent CMV infection with PCP increases the overall mortality of PCP from 14% to 92%. The mortality of CMV alone is 75% (3). To date there is no effective therapy for CMV pneumonia. Trials of DHPG (1, 3-dihydroxy-2 propoxymethyl guanine) have not shown any efficacy for CMV pneumonia (34-35).

M. TUBERCULOSIS

Since the first National Heart Lung and Blood Institute study of AIDS in 1984 the incidence of tuberculosis has increased (14). Tuberculosis now accounts for 7.7% of all pulmonary complications occurring in AIDS (32). Tuberculosis in AIDS occurs most frequently in Haitians and intravenous drug abusers. Haitians with AIDS have a 60% incidence of tuberculosis, and intravenous drug abusers have a 15% incidence of tuberculosis. Of those with tuberculosis, 60-70% have extrapulmonary involvement. (32-33)

The radiographic manifestations of tuberculosis in AIDS are reminiscent of primary tuberculosis. Cavitary disease does not occur in this setting. The middle and lower lobes are involved in 29% of cases, while the upper lobes are involved in only 18%. Hilar and mediastinal adenopathy is present in 59% of patients. No infiltrates are noted in 35% of patients (6).

The diagnosis of tuberculosis in AIDS is easily made by sputum smears and cultures, or bronchoscopy. The PPD will be positive in 40% of AIDS patients with tuberculosis (14).

For AIDS patients with a positive PPD and a normal chest radiograph, isoniazid chemoprophylaxis is recommended. For patients with active tuberculosis, isoniazid 10-15 mg/kg/d (300 mg/d) and rifampin 10-15 mg/kg/d (600 mg/d) are recommended for a minimum of nine months of therapy, and for 6 months after sputums become negative. In addition, ethambutol 25 mg/kg or pyrazinamide 20-30 mg/kg are recommended for the first 2 months of therapy. If either isoniazid or rifampin is not used, therapy should be extended to a minimum of 18 months, and for 12 months after sputums become negative (31).

FUNGAL INFECTIONS

Previously pulmonary fungal infections in AIDS have been infrequently reported (2,3). Recently disseminated histoplasmosis has been added to the list of opportunistic infections diagnostic of AIDS. Pulmonary cryptococcosis has been reported in 20% of patients in one small series (44). The true incidence is probably lower as primary cryptococcosis was reported in only 7.5% of 8000 patients in a retrospective review (45). Pulmonary cryptococcosis presents with fever, cough, pleuritic chest pain and hypoxemia. Pleural effusions are common. Radiographically, localized and diffuse infiltrates, as well as mediastinal adenopathy and cavities have been described. Antifungal therapy stabilizes but does not cure pulmonary cryptococcosis, and most patients die of disseminated fungal disease (44-46). Recently, coccidioidomycosis has been reported in AIDS. Here again nearly all patients suffer from disseminated disease. Antifungal therapy is effective in stabilizing disease progression, but nearly all patients die (47).

BACTERIAL PNEUMONIA

AIDS is known to be associated with defects in B-cell regulation as well as defects in cell-mediated immunity. Recently, Polsky and colleagues reported an increase in bacterial pneumonia in AIDS patients (36). On review of 176 pneumonia cases in AIDS patients they found a 10.2% incidence of bacterial pneumonia. The attack rate of pneumococcal pneumonia in their retrospective review was 17.9/1000 compared with an attack rate of 2.6/1000 in a general population ($P < 0.001$). Radiographic findings were equally divided between diffuse infiltrates, patchy lobar infiltrates, and lobar consolidation. Hemophilus influenzae was isolated in 8 cases, Streptococcus pneumoniae in 6 cases, and Branhamella catarrhalis and group B streptococcus in 1 case each. No isolate was found in 2 cases, however the gram stain in each suggested Streptococcus pneumoniae. 16/18 patients were cured with appropriate antimicrobial therapy.

In summary, bacterial pneumonia occurs with increased frequency in AIDS patients, presumably secondary to defective humoral immunity. Bacterial pneumonia should be considered particularly in the setting of lobar consolidation, and appropriate empiric therapy should cover Hemophilus influenzae and Streptococcus pneumoniae.

PULMONARY KAPOSI'S SARCOMA

In autopsy series pulmonary Kaposi's sarcoma has been found in 32 to 48% of AIDS patients with cutaneous Kaposi's sarcoma. Symptoms include stridor, wheezing, and hemoptysis secondary to endobronchial involvement. Pleurisy is also common. Chest radiography reveals parenchymal nodules in most patients, and pleural effusions in 50%; hilar and mediastinal adenopathy may be present. Interstitial and alveolar infiltrates occur frequently and tend to parallel bronchovascular markings. Diagnosis is generally made at open lung biopsy or at autopsy. Pleural fluid analysis, pleural biopsy, and bronchoscopy with transbronchial biopsy are not helpful. Although endobronchial disease is noted in up to 83% of patients with pulmonary Kaposi's sarcoma, endobronchial biopsies are usually non-diagnostic (11-12, 37).

On histopathology, pulmonary Kaposi's sarcoma shows focal involvement with infiltrating spindle cells, mitotic figures, and vascular slits containing red blood cells. Unexpected pulmonary hemorrhage on open lung biopsy should also lead one to consider pulmonary Kaposi's sarcoma (38).

Treatment for pulmonary Kaposis's sarcoma is unsatisfactory. Untreated the disease has a median survival of 3.8 months (37). Use of combination chemotherapy and alpha interferon for disseminated Kaposi's sarcoma results in an 8 month median survival (39).

SUMMARY

Pulmonary complications occur in up to 50% of all AIDS patients. The majority of these complications are infectious. The projected increase in the incidence of AIDS and related disorders will ensure the involvement of a broad spectrum of physicians in the evaluation and care of AIDS patients. Currently, effective therapy is available for *Pneumocystis carinii* pneumonia, tuberculosis, fungal and bacterial infections in AIDS patients. Satisfactory therapy is currently lacking for *Mycobacterium avium* complex, cytomegalovirus, and for Kaposi's sarcoma. Clinical investigations are underway to evaluate improved therapy for *Pneumocystis carinii*, *Mycobacterium avium* complex, cytomegalovirus, and Kaposi's sarcoma. The ultimate solution lies in prevention of HIV infection, and in reconstitution of the immune system in AIDS.

PULMONARY COMPLICATIONS OF HIV INFECTION

A Opportunistic Infections Diagnostic of AIDS
  1. *Pneumocystis carinii* pneumonia
  2. Pulmonary toxoplasmosis
  3. Extraintestinal (e.g., pulmonary) strongyloidiasis
  4. Bronchopulmonary candidiasis
  5. Pulmonary cryptococcosis
  6. Disseminated histoplasmosis
  7. Disseminated *Mycobacterium avium* complex or *M. kansasii*
  8. Cytomegalovirus pneumonia
  9. Herpes simplex pneumonia

B HIV-Related Pulmonary Infections
  1. Tuberculosis
  2. Nocardiosis

C Presumed HIV-Related Pulmonary Disorders
  1. Pyogenic bacterial pneumonia
  2. Lymphoid interstitial pneumonitis[*]

D AIDS-Related Pulmonary Neoplasia
  1. Kaposi's sarcoma
  2. Non-Hodgkin's lymphoma

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[*] Diagnostic of AIDS when occurring in a child <13 yr of age with positive HIV antibody test.

ARRD 135: 1987

Types and Frequency of Pulmonary Disorders in 441 Patients with AIDS.

PULMONARY DISORDER	NO. OF PATIENTS
Pneumocystis carinii pneumonia	373
Without coexisting infection	255
With coexisting infection	118
Cytomegalovirus	50
Mycobacterium avium-intracellulare	37
Mycobacterium tuberculosis	15
Legionella	9
Cryptococcus	8
Other	3
Other pulmonary infections	93
M. avium-intracellulare	37
Cytomegalovirus	18
Cytomegalovirus/*M. avium-intracellulare*	5
Cytomegalovirus/cryptococcus	1
Pyogenic bacteria	11
Legionella	10
Fungi	6
M. tuberculosis	4
Herpes simplex	2
Toxoplasmosis	1
Kaposi's sarcoma	36

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Specific Pulmonary Diseases and Associated Mortality

Disease	Patients (percent)*	Mortality (percent)†
Infectious causes		
P. carinii	57	43
Without CMV	36	14
With CMV	21	92
CMV pneumonia	34	86
Without P. carinii	13	75
M. avium-intracellulare	21	0
Noninfectious causes		
Kaposi's sarcoma	13	88
Nonspecific pneumonitis	12	0
Adult respiratory distress syndrome	7	100
Pleural	10	67

* The percent of patients with this disease at any time in their course. If two or more abnormalities were present, the patient was counted in all categories.

† The percent of patients with this diagnosis who died and in whom the disease was considered to be the cause of death or a major contributing factor.

CMV = cytomegalovirus.

Am J Med 78: 1985

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PLEURAL DISEASES

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ANATOMY AND PHYSIOLOGY

The pleura are complex serous membranes that cover the lung parenchyma (visceral pleura) and the adjacent surfaces of the chest wall, mediastinum, and diaphragm (parietal pleura). The potential space between these two layers contains a thin layer of fluid containing protein (1-2gm/100u) and cells (about 2/3 mononuclear and 1/3 mesothelial). The parietal pleura is studded with large pores (stomata) connecting directly to lymphatics, and gets its blood supply from the systemic capillaries. The visceral pleura is fed by both systemic (bronchial arteries) and pulmonary sources; it is also covered with a plexus of lymphatic vessels and lymphoid nodules.

Pleural fluid is normally formed at the surface of the parietal pleura and absorbed through the visceral pleura. Movement of protein and fluid in and out of the pleural space, which is governed by Starling forces, is normally slow. Flow can increase, however, up to 30 times without development of large pleural effusions. In disease, the balance of entry and exit is upset, and often the visceral pleura may even contribute to the formation of pleural fluid. Transudates are formed from alterations of the hydrostatic-osmotic relationship while the pleural membranes remain unchanged. Many factors are involved in the formation of exudates, but the two most common are increased permeability of the pleural surfaces to protein, and decreased lymphatic flow from the pleural space. A third cause of exudative pleural effusion, curiously enough, is decreased pressure in the pleural space, which may occur secondary to mainstem bronchial obstruction with massive atelectasis, or trapped lung due to a collagenous peel. One might expect such an effusion to be transudative, and occasionally that proves to be true, but for unclear reasons it is more often exudative.

CLINICAL MANIFESTATIONS

On physical exam in a patient with a large pleural effusion, there may be mild outward bulging of the intercostal spaces and a lag in inspiration on the affected side. In the area of the effusion, there is decreased fremitus, increased dullness, and decreased transmission of breath sounds. The upper border of a pleural effusion is always somewhat vague to percussion, because the meniscus of the effusion is an upward-pointing wedge that blends imperceptibly into normal parenchyma. It is common to find increased fremitus and egophony in the vague zone due to compression of adjacent lung by the pleural fluid; for this reason, fremitus is more useful than percussion in defining the upper limit of an effusion prior to thoracentesis.

RADIOLOGY

Blunting of a costophrenic angle may represent pleural reaction or pleural fluid. 250-300 cc's is necessary to blunt the lateral costophrenic angle. When effusion is suspected, bilateral decubitus films should always be obtained. This not only detects "layering out" of the fluid, but also allows maximal visualization of other areas of the lung which may have been obscured by pleural fluid; it may also demonstrate a contralateral effusion, which may change the differential diagnosis. Pleural effusion may be very difficult to detect on the supine or recumbent film and, if present, may be appreciated only as a diffuse increase in density on the affected side.

Subpulmonic effusions also can be subtle, presenting with a sharp costophrenic angle. Findings on PA view include:

1. Loss of posterior sulcus black to grey transition.

2. Lateralization of the apparent hemidiaphragmatic apex.

3. Separation of the apparent diaphragm from the top of the gastric air bubble by >1 cm (left-sided effusions).

Phantom tumors are interlobar effusions usually found in the minor fissure, most commonly from congestive heart failure. It appears as a biconvex density that disappears with diuresis.

Ultrasound can be useful for examining the pleural space, especially to localize small, loculated collections of pleural fluid that do not layer fully on decubitus films. Ultrasound can also detect subpulmonic fluid, as well as subphrenic collections or masses. However, intervening air and bone make it difficult to define fully an extensive pleural abnormality, and the technique is quite "operator-dependent".

The quality of a CT exam, on the other hand, does not depend on the technical skill of the examiner. It also provides much more information about the underlying lung parenchyma and chest wall. Specific indications for CT in pleural disease include:

- distinguishing lung abscess from empyema, when the latter is associated with gas-forming organisms, or with a bronchopleural fistula.

- defining suspected loculated fluid collections when additional information about the rest of the thorax is needed.

- to define extent and involvement of mesothelioma and select a site for biopsy.
- to evaluate postoperative pleural complications (when plain radiography is limited).

DIAGNOSTIC PROCEDURES

Only 25% of pleural effusions are resistant to diagnosis. Once pleural fluid is detected and localized, its cause should be determined; exceptions might be when the clinical diagnosis is secure, such as in congestive heart failure, or when only a small amount of pleural fluid is present. Even in congestive failure, the effusion should be tapped if it is unilaterally (especially left-sided), pleurisy or fever is present, heart size is normal, there is fever, or hypoxemia is disparately severe. Techniques for obtaining fluid and tissue are discussed elsewhere.

PLEURAL FLUID ANALYSIS

Generally 35-50cc of fluid is necessary for a complete analysis. It is probably cost-effective to order total protein, LDH, WBC count and differential, pH and glucose in all cases. Concomitant serum total protein, LDH, and glucose should be done. ABG should be drawn if the pleural fluid pH is <7.30. Gram stain, AFB stain, and cultures should be obtained only if infection is suspected. Pleural fluid cytology (specimen must be stored with added heparin) should be requested when malignancy is suspected or for any exudate of unknown cause. Lipid studies should be reserved for milky effusions. A pleural fluid amylase should be sent off only when pancreatitis, pseudocyst, or esophageal rupture is suspected, or there is a unilateral left sided effusion of unknown cause.

A. Appearance

Pleural fluid generally appears amber, or a straw color. A grossly blood effusion in the absence of trauma suggests infarction or malignancy, but keep in mind that as little as 2cc of blood from a traumatic tap can cause the effusion to appear serosanguinous, and give an RBC count of 5000-6000/mm^3. A putrid, thick, purulent effusion is characteristic of anaerobic empyema. A viscous, opaque fluid occurs in the presence of malignant mesothelioma due to high levels of hyaluronic acid. "Anchovy paste" fluid results from rupture of an amebic abscess from the liver into the right pleural space; black fluid may be seen in empyema from *Aspergillus*. Passage of a "flexible" nasogastric feeding tube inadvertently into the pleural space will cause an effusion of the same color as the dye in the feeding.

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Pleural fluid may appear "milky" in the following situations:

1. Pyothorax - if centrifuged, supernatant will be clear

2. Chylothorax - if allowed to stand, layering occurs with appearance of "cream".

3. Pseudochylous effusion - (to be discussed in a later section).

B. Transudate versus exudate

Current criteria to differentiate transudate from exudate include:

1. Pleural fluid to serum protein ratio ≥ 0.5

2. Pleural fluid to serum LDH ratio ≥ 0.6, or

3. Pleural fluid LDH ≥ 2/3 of upper limit of normal for serum LDH (usually ~ 200).

Only one of the above criteria need be present for the fluid to be an exudate. None should be present if the fluid is a transudate. If only a small amount of pleural fluid is obtained, a urine hydrometer may be used to test the specific gravity. A reading of 1.020 corresponds to 3.0 gm. protein and each .004 deviation represents a gram of protein. Use of the above criteria will "correctly" classify 99% of pleural effusions. Classification (exudate versus transudate) is important because the different pathologic processes involved create two more or less separate differential diagnoses (see tables). In general, once a pleural effusion is known to be transudative, further diagnostic studies are unnecessary; treatment is directed to the underlying disease. Exudative effusions, however, require a more extensive evaluation. It should be emphasized that the above classification criteria are not perfect. For instance, 10% of malignant effusions may be transudative; and a long standing transudate from CHF may turn exudative with diuretic therapy due to increased protein content (3).

Differential Diagnoses of Pleural Effusions

I. TRANSUDATIVE PLEURAL EFFUSIONS

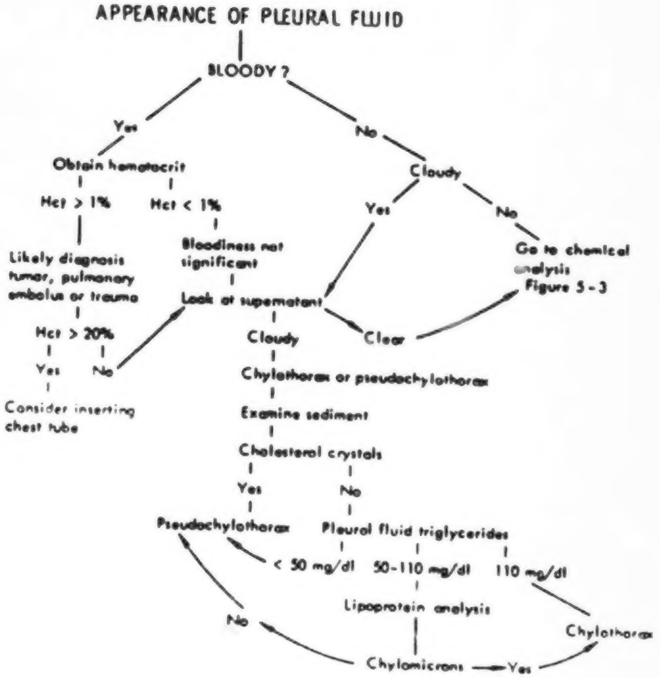
A Congestive heart failure
B Cirrhosis
C Nephrotic syndrome
D Peritoneal dialysis
E. Glomerulonephritis
F. Myxedema
G. Pulmonary emboli
H. Sarcoidosis

II. EXUDATIVE PLEURAL EFFUSIONS

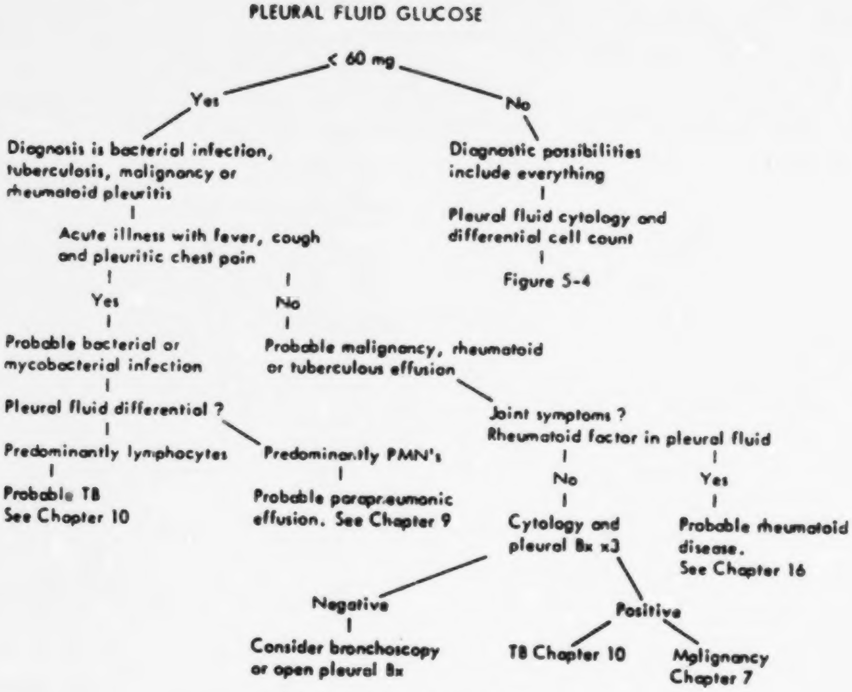
A Neoplastic diseases
    1. Metastatic disease
    2 Mesothelioma
B Infectious diseases
    1. Bacterial infections
    2. Tuberculosis
    3 Fungal infections
    4 Parasitic infections
    5 Viral infections
C Pulmonary embolization
D Gastrointestinal disease
    1 Pancreatitis
    2 Subphrenic abscess
    3 Intrahepatic abscess
    4 Esophageal perforation
    5 Diaphragmatic hernia
E Collagen vascular diseases
    1 Rheumatoid pleuritis
    2 Systemic lupus erythematosus
    3 Drug-induced lupus
    4 Immunoblastic lymphadenopathy
    5 Sjogren's syndrome
    6 Familial Mediterranean fever
    7 Wegener's granulomatosis
G. Drug-induced pleural disease
    1. Nitrofurantoin
    2. Dantrolene
    3. Methysergide
    4. Bromocriptine
    5. Procarbazine
    6. Methotrexate
    7. Practolol
H Miscellaneous diseases and conditions
    1 Asbestos exposure
    2. Postpericardiectomy or postmyocardial infarction syndrome
    3 Meigs' syndrome
    4 Yellow nail syndrome
    5 Sarcoidosis
    6. Uremia
    7. Trapped lung
    8. Radiation therapy
    9. Electrical burns
    10 Urinary tract obstruction
    11. Iatrogenic injury
I. Hemothorax
J. Chylothorax

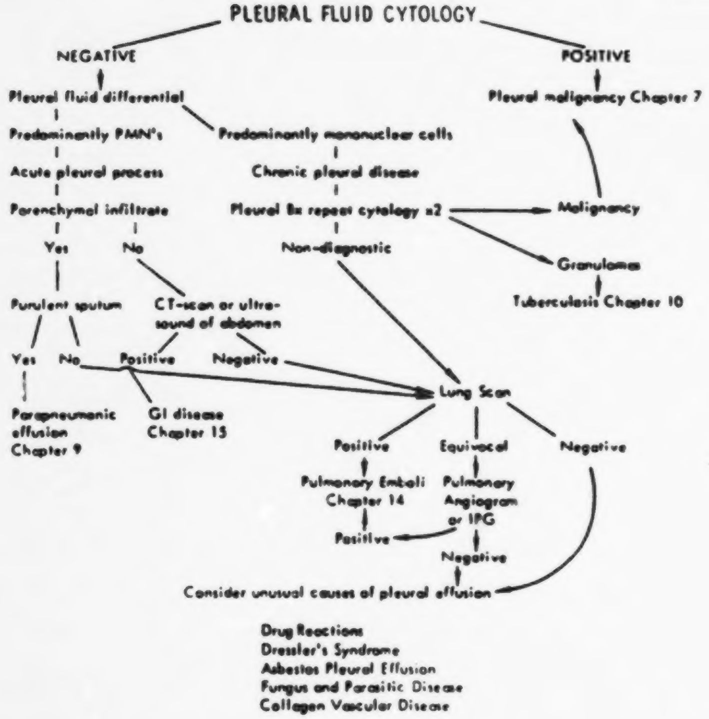
Approximate Annual Incidence of Various Types of Pleural Effusions in the United States

Congestive heart failure	500,000
Pneumonia (bacterial)	300,000
Malignant disease	200,000
Lung	60,000
Breast	50,000
Lymphoma	40,000
Other	50,000
Pulmonary embolization	150,000
Pneumonia (viral)	100,000
Cirrhosis with ascites	50,000
Gastrointestinal disease	25,000
Collagen vascular disease	6,000
Tuberculosis	2,500
Asbestos Exposure	2,000
Mesothelioma	450


APPEARANCE OF PLEURAL FLUID
BLOODY ?
Yes
No
Obtain hematocrit
Hct > 1%
Hct < 1%
Likely diagnosis tumor, pulmonary embolus or trauma
Bloodiness not significant
Hct > 20%
Yes
No
Consider inserting chest tube
Look at supernatant
Cloudy
Yes
No
Go to chemical analysis Figure 5-3
Cloudy
Clear
Chylothorax or pseudochylothorax
Examine sediment
Cholesterol crystals
Yes
No
Pseudochylothorax
Pleural fluid triglycerides
< 50 mg/dl
50-110 mg/dl
110 mg/dl
Lipoprotein analysis
Chylothorax
No
Chylomicrons
Yes

From Light RW: Pleural Diseases, 1983, page 62-63


PLEURAL FLUID GLUCOSE
< 60 mg
Yes
No
Diagnosis is bacterial infection, tuberculosis, malignancy or rheumatoid pleuritis
Diagnostic possibilities include everything
Pleural fluid cytology and differential cell count
Figure 5-4
Acute illness with fever, cough and pleuritic chest pain
Yes
No
Probable bacterial or mycobacterial infection
Probable malignancy, rheumatoid or tuberculous effusion
Pleural fluid differential ?
Joint symptoms ?
Rheumatoid factor in pleural fluid
Predominantly lymphocytes
Predominantly PMN's
No
Yes
Probable TB
See Chapter 10
Probable parapneumonic effusion. See Chapter 9
Cytology and pleural Bx x3
Probable rheumatoid disease.
See Chapter 16
Negative
Positive
Consider bronchoscopy or open pleural Bx
TB Chapter 10
Malignancy Chapter 7


PLEURAL FLUID CYTOLOGY
NEGATIVE
POSITIVE
Pleural fluid differential
Pleural malignancy Chapter 7
Predominantly PMN's
Predominantly mononuclear cells
Acute pleural process
Chronic pleural disease
Parenchymal infiltrate
Pleural Bx repeat cytology x2
Malignancy
Yes
No
Non-diagnostic
Granulomas
Tuberculosis Chapter 10
Purulent sputum
CT-scan or ultra-sound of abdomen
Yes
No
Positive
Negative
Lung Scan
Parapneumonic effusion Chapter 9
GI disease Chapter 15
Positive
Equivocal
Negative
Pulmonary Emboli Chapter 14
Pulmonary Angiogram or IPG
Positive
Negative
Consider unusual causes of pleural effusion
Drug Reactions
Dressler's Syndrome
Asbestos Pleural Effusion
Fungus and Parasitic Disease
Collagen Vascular Disease

From Light RW: Pleural Diseases, 1983, page 64-65.

C. Cell Count

Cell counts are actually of limited value. Suspected hemothorax can be confirmed by a pleural fluid to blood hematocrit ratio of >50%. If present, usually closed tube thoracostomy should be performed. A pleural fluid hematocrit of <1% is nonspecific. A hemorrhagic pleural fluid, by definition, contains at least 100,000 RBCs/mm3; it suggests infarction, neoplasm, or trauma. Only one-third of pulmonary infarctions, however, are attended by bloody effusion (4).

The total WBC count is also of little use. High counts are roughly associated with exudates. The differential WBC count is more valuable, however, though some authors disagree. Pleural neutrophilia suggests acute inflammatory diseases such as empyema, infarction, lupus pleuritis, pancreatitis, and some tuberculous effusions. Mononuclear cells (lymphocytes >50%) predominate in transudative effusions, and in chronic exudative effusions from malignancy, TB, or rheumatoid disease. Pleural eosinophilia may be seen in patients with paragonimiasis or benign asbestos effusions; however, the most common reason for eosinophilia is prior blood or air in the pleural space, especially from an earlier tap. Mesothelial cells normally constitute at least 5% of the differential; 1% or fewer suggests tuberculosis, but also occurs in malignancy and parapneumonic effusions (5). The presence of LE cells is a specific though insensitive marker for lupus pleuritis. Pleural fluid basophilia, while quite rare, indicates leukemic involvement.

D. Glucose

Low pleural fluid glucose (defined as pleural fluid/serum glucose ratio <1/2) is often associated with empyema, complicated parapneumonic effusions, and extensive pleural malignancy. Although once associated with tuberculosis, only 20% of tuberculous effusions have a glucose $\leq$ 30mg% (6). A very low pleural fluid glucose is characteristic of rheumatoid pleural effusions.

E. Amylase

Pleural fluid amylase levels of >160 Som. U/dl (or twice the serum value) suggest acute/chronic pancreatitis, malignancy or esophageal rupture (6). Esophageal rupture should be suspected when pleural fluid pH is very low (<6), and can be confirmed by fractionating the amylase.

F. pH

This should be collected anaerobically on ice, and assayed immediately. This is best done on a blood gas analyzer, but should not be done (and does not need to be done) if the fluid is grossly purulent. Pleural fluid acidosis is defined as a pH <7.30, or 0.15 less than the serum pH in acidemic patients. This can be found in empyema, esophageal rupture, malignancy, TB, hemothorax, pancreatic pseudocyst, collagen vascular disease, and incarcerated diaphragmatic hernia.

In patients with a clinical picture of pneumonia with parapneumonic effusion, thoracentesis should be performed if the pleural thickness appears greater than 10mm on decubitus films. In such patients, chest tubes should be placed promptly if the tap shows any of the following characteristics:

1. Gross pus
2. Organisms on gram stain (an honest, diligent, 20 minute search is crucial)
3. Pleural fluid glucose level $\leq$30-40 mg/dl (except in patients with rheumatoid or malignant effusions)
4. pH < 7.0

If the pleural fluid pH is $\geq$ 7.20 or the LDH is <1000, no therapeutic maneuvers need be performed. Those with pleural fluid pH between 7.00 and 7.20 or LDH $\geq$ 1000 must be watched closely. If the pleural effusion is initially large, with pH close to 7.0, chest tube drainage is probably indicated. Otherwise, effusions with these intermediate values may be evaluated frequently with serial chest x-rays and repeat thoracentesis.

G. Cytology

If malignant pleural effusion is suspected but initial cytology is negative, at least two more specimens should be submitted for cytology. Both Pap smears and cell block fixing should be performed; Pap smears are more sensitive, but reactive mesothelial cells may be misread as malignant. Cytologic exams as described will result in a diagnostic sensitivity of 90+% with three thoracenteses(8). Very little additional yield is afforded by pleural biopsy, but on rare occasions biopsy may be positive when cytology is negative. (The converse is true in primary tuberculous effusions, where pleural biopsy has a much higher yield than pleural fluid.)

When cytology is negative three times, chromosomal analysis of the fluid will occasionally detect malignancy, especially lymphoma, leukemia, or mesothelioma. The most common reason for negative cytology in effusions related to malignancy is that the fluid in question is not due to pleural seeding but rather to obstruction of mediastinal lymphatics.

H. Other Tests

LE cells can be found in both drug-induced and idiopathic SLE. Total complement, C3 and C4 levels are commonly decreased in rheumatoid and lupoid pleural effusions (9). Rheumatoid factor may be high in rheumatoid effusions, but this is quite nonspecific, since high levels may also be found in carcinomatous, tuberculous, and parapneumonic effusions (9).

I. Lipid

Milky or opalescent fluid suggests the presence of lipid. Persistence of cloudy supernatant after centrifugation confirms it. Chylothorax is usually right sided, since the greater portion of the thoracic duct traverses the right hemithorax. Only a small portion arches leftward with the aorta. Chylous fluid can be affected by dietary changes, and may appear watery and thin after surgery. Left sided chylous effusions occur more often after cardiovascular surgery. Chylous effusion may not appear for a week after surgical or traumatic disruption of the thoracic duct. Lymphoma can present as a chylous effusion without mediastinal adenopathy. Lymphangiomyomatosis, a rare disease of young women, is associated with chylous effusion and spontaneous pneumothorax. Chylous effusions generally contain >400mg/dl lipids, with triglyceride level $\geq$ 110mg/dl, or twice the serum value. If levels are slightly below this, then lipoprotein electrophoresis demonstrating chylomicrons confirms the chylous nature of the fluid. Pseudochylous effusions, although characterized by high phospholipid and cholesterol levels, contain no chylomicrons, and have low triglyceride levels (usually less than 50 mg/dl) (12). They may occur with marked malnutrition and in long-standing rheumatoid or tuberculous effusions.

TRANSUDATIVE EFFUSIONS

The diagnostic criteria for transudates have been previously discussed. They occur when the systemic factors acting on the formation/absorption of pleural fluid are changed, resulting in fluid accumulation. These factors include 1) increased systemic capillary pressure, 2) increased pulmonary capillary pressure, 3) decreased intravascular oncotic pressure, or occasionally 4) more negative pleural pressure. According to one large study (7), 72% of patients with congestive heart failure had pleural effusions; of these, 88% had bilateral pleural effusions. Of the 12% with unilateral effusion 2/3 were right sided and 1/3 left sided. The main point is that a unilateral pleural effusion should not be ascribed to congestive heart failure unless it is demonstrated to be transudative. If the effusion is bilateral, clinical judgment can dictate the need for thoracentesis. It should be added that 60% of patients with constrictive pericarditis develop transudates, of which more than half are bilateral and the rest right-sided (13).

Pleural effusions are observed in 5-6% of patients with hepatic cirrhosis and ascites (14) (never in patients without ascites). Two thirds of these effusions are right sided; the remainder are either left sided (16%) or bilateral (16%). The effusion can be large, and cause acute dyspnea. The transudative fluid is often blood-tinged or even bloody, but this has no significance. The treatment of these effusions should be directed toward the treatment of the underlying ascites, since the cause of the effusion is transdiaphragmatic transport of ascitic fluid (15). In refractory cases, pleurodesis may be attempted.

About 20% of patients with nephrotic syndrome have pleural effusions, frequently subpulmonic in location. Although most of these are transudative due to lowered plasma oncotic pressure, a diagnostic tap should be performed; an exudative effusion suggests pulmonary embolism which is not unusual in these patients (16). Light believes that all patients with nephrotic syndrome and pleural effusion should have lung scans, since 20% of effusions that occur with pulmonary emboli are transudates (17).

PARAPNEUMONIC EFFUSIONS AND EMPYEMA

About 40% of patients with bacterial pneumonia will have a pleural effusion, making this the most common cause of an exudative pleural effusion (18). Initially, the pneumonic process leads to increased permeability of the visceral pleural capillaries and the accumulation of a sterile pleural effusion. Subsequently, especially if the infection is untreated, the previously sterile fluid becomes infected with bacteria, causing a lowering in pH and glucose, increased LDH, increased PMN's, and massive fibrin deposition over the pleural surfaces, making drainage difficult. In the resolution stage, this fibrin layer may thicken and encase the lung (pleural peel), impairing respiratory function. Although parapneumonic effusions are common with aerobic pneumonias, antibiotic therapy has reduced the incidence of empyema due to these organisms. Anaerobic infections are the leading cause of empyema nowadays, occurring in about 35% of all anaerobic pneumonias (19). Indications for chest tube drainage in parapneumonic effusions have been previously discussed.

MALIGNANT PLEURAL EFFUSIONS

The most common cause of long standing exudative pleural effusion is malignancy, especially adenocarcinoma (20). Together, lung, breast, lymphoma, and ovarian carcinoma account for about 80% (21). The most common mechanism is probably decreased clearance of protein from the pleural space due to obstruction of lymphatic stomata in the parietal pleura.

Thoracic duct or mediastinal node involvement may also hinder protein clearance through the lymphatics. A less common mechanism is through an increase in negative pleural pressure when atelectasis occurs from bronchial obstruction. Cytology is frequently negative in pleural effusions arising from either of the last two mechanisms (22).

Pleurodesis should be performed in those individuals who rapidly reaccumulate malignant pleural fluid which is causing significant respiratory embarrassment. The ideal agent for pleurodesis is tetracycline, which is effective in >80% of selected cases. Other agents, such as nitrogen mustard and quinacrine, have been shown to be less effective and/or more toxic. Although historically a painful procedure, pleurodesis can be accomplished with minimal pain by the following steps (23-24):

1. Perform a tube thoracostomy in the posterior axillary line. Tube thoracostomy is often inadvertently performed in the wrong place. One should insist on the eighth or ninth interspace. Insure radiographically that the chest tube ports are in the most dependent portions of the pleural space.

2. Attach the chest tube via a water seal to gentle suction, i.e. - 15 to -20 cm water, and maintain suction until the pleural space is radiographically "dry" (usually for 24 hours or until drainage has stopped).

3. Mix 1000 mg (15-20mg/kg) of tetracycline with 70cc of sterile water and 15cc of 1% lidocaine (150 mg lidocaine).

4. Prep the chest tube, cross clamp distal to the prepped site and inject the mixture into the chest tube. Follow the injection with another injection of 200 cc's of air. Put tape over the injection holes in the tube.

5. Rotate the patient into right lateral decubitus, left lateral decubitus, prone and supine positions for 3 minutes each followed by the same positions for 30 minutes each.

6. After two hours unclamp the chest tube and return to negative pressure.

7. The tube may be removed when drainage is less than 150cc/24 hours and chest appears radiographically "dry".

Pleurodesis may not be effective if initial pleural fluid glucose and/or pH is low, since these values may represent extensive metastatic implants on the pleural surface. Likewise, a lung that appears "trapped" after initial thoracentesis will not respond, and chemical pleurodesis should not be attempted.

Talc poudrage is an alternative bedside technique that is associated with good results and low morbidity (26).

If simpler methods fail pleurectomy should be considered in those in relatively good condition with an extended prognosis (27); such a patient is a distinct rarity, but an occasional patient with breast cancer may fit these criteria.

TUBERCULOUS EFFUSIONS

Tuberculosis causes two types of pleural effusion. One is tuberculous empyema, a complication of extensive pulmonary disease which is rare nowadays; empyema occurs when a parenchymal focus ruptures through the visceral pleura to form a bronchopleural fistula. Management includes chemotherapy and drainage, in that order. Since pleurocutaneous fistula is a chronic complication when a chest tube is placed into an untreated tuberculous empyema, treatment with antituberculous drugs for 6 weeks should precede tube thoracostomy.

The more common type of effusion is that seen within 6 months of primary infection with tuberculosis, often in the absence of other x-ray evidence of pulmonary disease. These effusions are thought to be produced by small quantities of AFB reaching the pleural space from an adjacent caseous focus or from bacteremia. Delayed hypersensitivity from sensitized pleural lymphocytes, not extensive pleural infection, is thought to be the etiology of the effusion (25).

Although tuberculosis is usually considered a chronic illness, tuberculous pleuritis presents acutely in 2/3 of cases, usually with cough and chest pain (26). The chronic form involves low grade fever and weight loss. In general, patients with tuberculous pleuritis are younger than those who present with parenchymal TB, although recently this distinction has been less evident. The effusions are most often moderate in size, and are almost always unilateral (27). Despite the fact that the effusion is felt to be a hypersensitivity phenomenon, skin tests are negative in 30% of tuberculous pleuritis, especially in older patients. (28) The exudate very rarely contains acid-fast organisms or yields a positive culture (<25%) (29). Other characteristics of the fluid were discussed in a previous section.

The most helpful diagnostic procedure is pleural biopsy. The initial biopsy will show caseating granulomas with organisms in about 60% of cases (29). Two additional biopsies, with culture, will bring the diagnostic yield to 90+% (30).

It should be noted that despite the usefulness of pleural biopsy, a negative result does not rule out tuberculous effusion. To quote Richard Light (31), "If the skin test is positive, the only way to exclude the diagnosis of tuberculous pleuritis is to grind up the entire patient and inject him into an army of guinea pigs or to perform open thoracotomy. Because the patient usually refuses the first alternative ... patients with undiagnosed exudative pleural effusions and a positive PPD test should be treated for pleural tuberculosis".

Untreated, most tuberculous pleural effusions will resolve within weeks to months, with only rare development of restrictive pleural fibrosis. However, 2/3 of patients will develop overt pulmonary TB within 5 years if untreated (31). A nine-month course of INH and rifampin is usually adequate. Once a diagnosis is made, and definitive therapy begun, steroids can safely speed relief of symptoms and fluid resorption.

FUNGAL-PARASITIC-VIRAL EFFUSIONS

Most fungi that cause pulmonary disease, such as histoplasmosis, blastomycosis, and cryptococcosis, rarely cause pleural effusions. 5-10% of symptomatic patients with primary coccidioidomycosis will have pleural effusions (32), presenting with fever and pleurisy. Pleural fluid cultures are positive in almost all cases (32). The effusion is self-limited; treatment is only necessary if there is evidence of dissemination. Occasionally, in a patient with chronic cavitary coccidioidomycosis, the cavity will rupture into the pleural space, creating hydropneumothorax. These patients should be treated with chest tube drainage and systemic anti-fungal therapy (33).

The two "fungi" (actually higher bacteria) that regularly produce pleural effusions are Actinomyces and Nocardia. Actinomycosis, usually arising from infected gums, carious teeth, or exogenously from steam ducts, involves the pleura in 50% of cases. It has a tendency to form subcutaneous abscesses after burrowing through the chest wall. The purulent effusion is characterized by "sulfur granules." On gram stain, these granules are composed of slender, gram-positive, long, branching filaments. Anaerobic cultures will be positive. Penicillin is the treatment of choice. Nocardia appears similar on gram stain, but is a slow growing aerobic organism. There is less sinus tract formation, and most affected patients are immunosuppressed. Trimethoprim-sulfamethoxazole is probably the drug of choice. In both of these diseases, if the effusion is serous and lymphocytic, medical therapy alone is adequate; if frank pus is apparent, tube thoracostomy should be performed.

Pleural effusions due to hepatic amebiasis arise by either of two mechanisms. A sympathetic right sided effusion can result from diaphragmatic irritation, in a similar manner to effusions associated with pyogenic liver abscesses (34). On the other hand, an amebic abscess can rupture through the right hemidiaphragm, producing the classic "chocolate sauce" or "anchovy-paste" appearance on thoracentesis. Amebic trophozoites can be demonstrated in the fluid. Intrapleural rupture of an amebic abscess requires wide bore chest tube drainage in addition to therapy with metronidazole.

Paragonimiasis, the most common cause of hemoptysis in some countries, commonly involves the pleura. Bilateral disease is seen in half the patients. Pleural fluid will be exudative with low glucose, low pH, high LDH, and many eosinophils (35). Although bithionol is the drug of choice, there may be insufficient penetration in long standing cases, making decortication necessary.

Viral infections probably cause pleural effusion more than we realize, since the effusions are generally self-limited and acute/convalescent serological tests are usually not performed. The estimated prevalence of pleural effusion in primary atypical pneumonia is probably about 20%, though the majority are small and visible only on lateral chest x-ray. Mycoplasma may occasionally produce a large effusion.

IMMUNOLOGIC AND DRUG-INDUCED PLEURAL DISEASE

Clinical evidence of rheumatoid pleurisy occurs in about 5% of patients with rheumatoid disease; the rate of asymptomatic pleural involvement approaches 50% (36). Pathologically, rheumatoid nodules appear on the visceral pleura, with subsequent fibrosis. It generally occurs in males with subcutaneous nodules (37). Although concomitant exacerbation of peripheral arthritis is frequent, fever is unusual and pleuritic chest pain is uncommon. The pleural exudate exhibits the characteristic triad of low glucose, low pH, and high LDH. Pleural fluid complement levels may be low, and rheumatoid factor high, but these findings are less reliable. The effusion is unilateral in 75%, and also resolves spontaneously within 3 months in 75%, with a recurrence rate of 33%. The goal of therapy is to prevent progressive pleural fibrosis that would require decortication, but the efficacy and safety of treatment is unclear. The chief difficulty is that rheumatoid effusions have a tendency to become infected; because of the nature of these effusions, the resultant empyemas are sometimes underdiagnosed unless careful gram stains and aerobic/anaerobic cultures are done. Light recommends an 8-12 week trial of NSAID's, followed by reassessment. If the inflammatory process is worsening, a trial of alternate day steroids is warranted, with careful monitoring (38).

SLE involves the pleural space in up to 75% of patients at some point in the course of their disease (36). The patients are usually female. Fever is common (50%), and in contrast to rheumatoid effusion pleuritic chest pain is typical. Frequently the effusion is bilateral (about 50%). Seventeen percent of the time it will alternate from side to side. Like rheumatoid effusions, the exudate of lupus pleuritis has low complement levels. Unlike rheumatoid disease, however, the pleural fluid glucose and pH will be normal or nearly so. Additional helpful tests are the pleural fluid ANA (somewhat sensitive and very specific) and the presence of LE cells in the fluid (rarely positive, but very specific). Steroids provide effective treatment, in contrast to rheumatoid pleuritis.

In addition to several drugs which may cause pleural disease through induction of a lupus-like syndrome, a number of drugs can cause primary pleural toxicity (36). Nitrofurantoin (Macrodantin) causes an acute hypersensitivity pleuropulmonary reaction in 5-25% of treated patients; of these, 20% have unilateral pleural effusion. Over 80% will have peripheral eosinophilia and lymphopenia. Methysergide (Sansert) causes a slowly progressive pleuropulmonary fibrosis in about 0.5% of patients, probably due to direct stimulation of fibroblasts. Fever, weight loss, and pleurisy are common. Procarbazine causes an acute hypersensitivity pleuropulmonary reaction with eosinophilia and bilateral pleural effusions; the syndrome is rapidly reversible with withdrawal of the drug. Dantrolene infrequently can cause an acute non-lupus-like pleuritis with fever, chills, malaise, and pleuritic chest pain, months to years after initiation of therapy. Unilateral effusions and peripheral and pleural fluid eosinophilia have been consistently observed to date. Other drugs can cause pleural effusions, usually in concert with a more clinically important interstitial pneumonitis; some examples are mitomycin, bleomycin, amiodarone, and methotrexate.

POST CARDIAC INJURY SYNDROME

This, is an immunologically mediated disorder consisting of fever, pleuritis, pericarditis, and pulmonary infiltrates three weeks after injury/surgery to the pericardium or myocardium (39). It has occurred in the clinical setting of MI, cardiac injury, blunt chest trauma, and pacemaker implantation. Although it occurs in only 1% of MI patients, it affects 30% of post-cardiac surgery patients (40). The pleural fluid (in the 85% or so with effusions) is typically serosanguinous with a high glucose and pH (36). The syndrome clinically resembles pulmonary embolism, but hemoptysis is never seen. Differentiation, of course, may require lung scan and/or pulmonary angiogram. Treatment of " Dressler's syndrome" is often unnecessary, as the disease is self-limited. NSAID's have been useful. Those with severe symptoms (especially post-CABG patients) should be treated with steroids for several months, followed by a slow taper (41).

ASBESTOS -RELATED PLEURAL DISEASE

The pleura are more commonly affected by asbestos fibers than is the lung parenchyma. It is the fibrous nature of asbestos, not the minerals themselves, that apparently mediates the pathogenic effect. For example, in Turkey the nonasbestos-fiber erionite has been extensively used in two small villages as a building material. In these communities, pleural plaques are very common, and mesothelioma is one of the leading causes of death (42).

The spectrum of disease related to asbestos is broad. Pleural plaques are shiny, white elevations of the parietal pleura with sharp borders, located laterally on the costal pleura, diaphragm, mediastinum, over the vertebrae, and sometimes on the pericardium. They develop gradually, becoming visible only after 20 years when they become calcified. Even then, the multiple, bilateral plaques are best seen end-on; they may be totally missed or mistaken for parenchymal lesions if viewed"en face". Fluoroscopy is generally more helpful than oblique views. CT can be helpful, especially in identifying plaques adjacent to the vertebrae. The clinical significance of pleural plaques is nil, except as a clinical marker for possible coexisting asbestos-related disease.

Benign asbestos pleural effusions, unlike pleural plaques, bear a direct relationship to the degree of asbestos exposure (10% in heavily exposed individuals) and usually occur within 5 years of the initial exposure (43). Most patients are asymptomatic; the most common symptom is a vague "chest heaviness". The effusion is unilateral in 90%, and over 50% have chest x-ray evidence of parenchymal asbestosis. The fluid is an exudate, often with high WBC counts and eosinophilia. It is of utmost importance to rule out tuberculosis, mesothelioma, bronchogenic carcinoma, and pulmonary embolism. Benign asbestos effusion is a diagnosis of exclusion. About 20% of patients will develop massive pleural fibrosis, termed "hyalinosis complicata" (42). CT scan will demonstrate fibrous strands ("crow's feet") penetrating the lung parenchyma from the thickened pleura. Sometimes the process traps a portion of the peripheral lung, the subsequent shrinking of fibrous tissue creating an area of "rounded atelectasis". Despite the often severe impairment of lung function, decortication is usually of no benefit because of the parenchymal involvement.

The most feared pleural complication of asbestos exposure is the development of diffuse malignant mesothelioma. It bears no relation to smoking, and usually develop 30 years or more after initial exposure. The tumor arises on the visceral and parietal surfaces of the pleura, invading the chest wall early and often encasing the lung in a thick rind. Lymph node and hematogenous spread occur late in the course. Patients with mesothelioma initially present with dyspnea and chest pain, accompanied by a large unilateral pleural effusion. More than half will have a history of asbestos exposure, but only 20% will have chest x-ray evidence of such (44). Diagnosis is made difficult by the fact that pleural fluid cytology is unreliable; malignant and reactive mesothelial cells are hard to distinguish, and often the cytologist will make a misleading diagnosis of metastatic adenocarcinoma from an unknown primary. Closed pleural biopsy is likewise difficult to interpret, and even new electron microscopy techniques have not added much. CT scanning can be highly suggestive of the diagnosis and should always be done, but most patients require an open pleural biopsy for diagnosis.

Survival is usually only 10-11 months after diagnosis. Patients usually succumb to progressive hypoxemia from shunting of blood through non-aerated lung, or to respiratory infections. Therapy is unsatisfactory. Surgical pleurectomy is palliative, ensuring adequate tissue for diagnosis, avoiding recurrent pleural effusions, and retaining maximum lung function and gas exchange. Chemotherapy is difficult to evaluate because of small numbers, but adriamycin-cisplatinum has shown promise, prolonging survival to 17-27 months in responders, with a few long term survivors (44). Radiation therapy to date has added little to the above except toxicity.

PNEUMOTHORAX

Pneumothorax is air in the pleural space, and can be classified as spontaneous, traumatic or iatrogenic. Primary spontaneous pneumothorax occurs in healthy individuals, usually tall, thin, male smokers. Susceptible individuals develop subpleural emphysematous blebs, which may rupture, creating acute pneumothorax. The resultant decreased pO2 and decreased vital capacity are well tolerated by most healthy patients; the presenting symptoms are dyspnea, and chest pain localized to the side of the pneumothorax. Most episodes occur suddenly at rest, and often the patient does not seek medical attention for several days. Physical exam reveals a moderate tachycardia, decreased thoracic wall motion, absent tactile fremitus, tympanitic percussion, and reduced breath sounds on the affected side. If the pulse is higher than 140, or if hypotension or cyanosis is present, a tension pneumothorax should be suspected. About 10-20% of patients will have a small pleural effusion. Diagnosis is made by recognizing the visceral pleural line on chest x-ray. The extent of a pneumothorax should be quantified since visual interpretation of the chest x-ray always underestimates the degree of collapse. The volumes of the lung and the hemithorax are proportional to the cube of their diameters. So, if the diameter of the hemithorax were 10cm, and the distance between the lung and the chest wall were 4 cm, then

$$\frac{d(\text{lung})^3}{d(\text{hemithorax})^3} = \frac{6^3}{10^3} = 22\%,$$ implying an 78% pneumothorax.

Non-invasive treatment should be reserved for pneumothoraces occupying less than 15% of the hemithorax. Only 1.25% of the volume of the hemithorax can be absorbed each day (46), and while high levels of supplemental oxygen do increase this rate of pleural air absorption, they do so to a variable extent. Most patients will require a chest tube, which should be inserted into the most superior portion of the pleural space, where the accumulated residual air can be evacuated rapidly. If persistent air leaks occur or if the lung remains unexpanded after 5 days of chest tube suction, open thoracotomy with oversewing of the subpleural blebs and pleural scarification should be considered. It should be pointed out that patients who present with symptoms of more than three days duration should not have suction applied to the chest tube because of the possibility of reexpansion pulmonary edema.

Of patients not treated with pleurectomy, over half will have an ipsilateral recurrence over the next 5 years (47). By the time of the third episode, an 80% recurrence over the next two years can be expected. Because of this high recurrence rate, tetracycline pleurodesis (technique outlined in a previous section) is presently being studied as a means of preventing further episodes; unfortunately, preliminary results have not been encouraging (Jenkinson, personal communication).

Secondary spontaneous pneumothorax is a more serious entity, since it occurs in patients with previously impaired lung function, most commonly due to COPD. Other diseases associated with this phenomenon include tuberculosis, sarcoidosis, lung abscess, primary bronchogenic carcinoma, metastatic pleural disease, asthma, scleroderma, eosinophilic granuloma, tuberous sclerosis, idiopathic pulmonary fibrosis, lymphangiomyomatosis, biliary cirrhosis, Marfan's syndrome, idiopathic pulmonary hemosiderosis, pulmonary alveolar proteinosis, pulmonary infarction, rheumatoid disease, berylliosis, and especially cystic fibrosis.

Clinical symptoms are similar to those seen in primary spontaneous pneumothorax, but are much more severe. Physical findings are less helpful, because of baseline abnormalities. The presence of chest pain in a patient with COPD and increasing dyspnea should raise clinical suspicion. Once diagnosis is confirmed by chest x-ray, a chest tube should be inserted immediately. Generally, 5 days are required for reexpansion of the lung, although ABG's improve within 24 hours and symptomatic relief may be immediate. About 25-30% of patients will require a second chest tube (48); if the lung remains unexpanded or a pleural air leak persists, open thoracotomy should be considered. Since recurrences in this group of patients are poorly tolerated, tetracycline pleurodesis may be considered with the initial presentation.

The most common cause of pneumothorax has become iatrogenesis, because of increased use of pulmonary diagnostic procedures, mechanical ventilation with high PEEP, and central line placement. Although the incidence of pneumothorax is only

4% in mechanically ventilated patients, it is greatly increased in the presence of the following clinical complications/conditions: aspiration pneumonia (37%), PEEP (15%), right mainstem intubation (13%), and COPD (8%) (45). In ventilated patients, pneumothorax is heralded by a sudden clinical deterioration. An increased peak airway pressure (decreased static compliance) is characteristic. A chest x-ray should be obtained promptly in any ventilated patient who develops an acute increase in peak airway pressure. When pneumothorax occurs in this setting, positive pressure ventilation prevents sealing of the air leak, hence tension pneumothorax can rapidly develop. If this is suspected, immediate insertion of a large bore needle into the second anterior intercostal space can be life-saving, by converting a tension pneumothorax to a simple pneumothorax. Chest tube placement should then follow promptly, and be left in place for at least 48 hours after the air leak stops.

The treatment of a procedure related- pneumothorax in the patient not on mechanical ventilation can be tempered by the fact that recurrence is unlikely. If the pneumothorax is small, and the patient minimally symptomatic, observation is all that is necessary.

Pneumothorax can follow blunt as well as penetrating trauma. In blunt trauma, forceful external compression of the lung will cause alveolar rupture, and interstitial/mediastinal emphysema. Pneumothorax occurs when the air ruptures through the pleura. All such pneumothoraces should be treated with tube thoracostomy. Hemoptysis, continued air leak after thoracostomy, or fracture of the 1st three ribs should prompt fiberoptic bronchoscopy to search for a bronchial or tracheal tear, which would necessitate surgical repair (49). A concomitant pleural effusion should be tapped; if the amylase is high and the pH low, esophageal rupture must be ruled out.

HEMOTHORAX AND FIBROTHORAX

Hemothorax is defined as frank bleeding into the pleural space, most frequently from trauma or complications of procedures such as central line placement or thoracentesis. Pleural effusions often appear to be bloody, but a hemothorax is present only if the hematocrit of the fluid is >50% of the peripheral hematocrit. The treatment is immediate placement of a large-bore chest tube. Concerns that the increased pleural pressure from a large hemothorax may be tamponading a bleeding vessel have been shown to be misplaced (50). Immediate tube placement, in allowing for more complete evacuation of blood from the pleural space, decreases the risk of subsequent empyema (blood is an excellent culture medium) and fibrothorax, and allows for ongoing measurement of further bleeding.

Management of unresolving hemothorax (residual blood in the pleural space) has classically been thoracotomy with decortication in 2-3 weeks, to remove clots before fibrosis has taken place. However, recent data has shown that the incidence of fibrothorax is < 1% even when residual blood is present, and the risk of empyema is not changed by thoracotomy (51). Probably open thoracotomy should be reserved for retained hemothorax that covers >30% of the hemithorax (52).

Fibrothorax is adherence of a fibrous layer or "peel" to the pleural surfaces, sometimes associated with calcification. Although the main causes are hemothorax and empyema, fibrothorax can also result from TB, pancreatitis, collagen vascular disease, and uremia; no etiology is found in at least half the cases. The presenting complaint is dyspnea on exertion, occurring when pulmonary function is severely depressed. Fibrothorax not only causes a restrictive ventilatory defect, but reduces perfusion on the affected side as well. Interestingly, the perfusion defect is often more severe than the ventilation defect (53). Such patients may develop pulmonary hypertension and cor pulmonale. The only treatment is decortication, a major surgical procedure with a mortality rate of close to 5% (54). It should not be performed in patients with a fibrous peel due to recent inflammatory disease (hemothorax, infection, or tuberculous pleuritis) since the pleural thickening in these settings often improves with time. Surgery should be reserved for symptomatic patients with a good functional status and without significant parenchymal lung disease, in whom pleural thickening has been stable or progressive on chest x-ray over at least a six month period (54).

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PULMONARY PRE-OPERATIVE EVALUATION

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PULMONARY PHYSIOLOGY IN THE POSTOPERATIVE PERIOD

Of all organ systems, the lung is the most likely to cause morbidity in the perioperative period, and with the exception of the heart the one most likely to cause postoperative mortality. Thus the lung occupies a position of crucial importance in assessing operative risk, and in minimizing postoperative complications. This chapter will discuss the effects of surgery on pulmonary function, lung diseases or conditions which increase morbidity in surgery, specific concerns in lung resection, and finally methods for perioperative prophylaxis.

Changes in Ventilation Patterns

It is common knowledge that postoperative pain in the chest or abdomen decreases sighing and coughing. Narcotic analgesia can, and probably often does, eliminate sighing and coughing altogether if the patient is not otherwise specifically instructed and encouraged. (1) However, judicious use of analgesics can enable deeper breathing and coughing. (2)

After non-abdominal surgery there are no consistent changes in vital capacity (VC) or lung volumes. (3,4) Accordingly, clinically significant respiratory complications are uncommon after non-abdominal surgeries. (3,5) Lower abdominal surgery is associated with a 25-30% decrease in VC and mild decreases in oxygenation, but these changes are usually not significant after postop day #1, and complications are significantly less common than with upper abdominal surgery. (3,5,6,7) Changes in VC and FRC post thoracotomy are similar to those of upper abdominal surgery except that mild impairments persist for a longer period of time after thoracotomy.(8,9,10) The rest of this section will be primarily oriented to the effects of upper abdominal surgery.

One of the earliest changes in postoperative ventilatory function after upper abdominal surgery is a marked decrease in vital capacity to 50-60% of the preoperative value. (10,11,12) Tidal volume is decreased by an average of 25%, accompanied by a 20% increase in respiratory rate resulting in no net change in minute ventilation. (3,13) The supine position alone accounts for a 10-20% reduction in lung volumes postoperatively. (4,11) These changes early in the postoperative course are followed by reductions in FRC and RV of about 30% at 16-24 hours postoperatively. (10,11)

Patients with the greatest reductions in FRC have been found to have the highest incidence of pulmonary complications. (11) In one study, all patients with an FRC reduction > 40% had clinical and radiographic evidence of atelectasis. (11) The reduction in FRC and clinical evidence of atelectasis is associated with postoperative hypoxemia. Indeed, atelectasis can be predicted by changes in A-a gradient very early in the postoperative course, long before the reduction in FRC occurs. (10,14)

Even accounting for changes due to the supine position, and if pain is eliminated by epidural block, marked decreases in VC and lung volumes will still occur after upper abdominal surgery. (15,16) General anesthesia cannot be implicated since non-abdominal surgery with general anesthetic does not cause these changes postoperatively. (3,5)

Diaphragmatic Dysfunction

It has long been suspected that diaphragmatic dysfunction was a primary etiology for the changes in lung volumes after upper abdominal surgery and recent work has confirmed it. An early fluoroscopic study showed decreased diaphragmatic excursion postoperatively with proportional decreases in VC. (17) Ford et al assessed diaphragmatic function pre and postoperatively in 10 patients undergoing cholecystectomy, by magnetometer measurements of abdominal and rib cage excursions and transdiaphragmatic pressure swings. (13) Results indicated marked decreases in the diaphragm's contribution to tidal breathing.

In a later study it was shown that pain was not the cause of the alteration in diaphragm function, since epidural anesthesia did not improve transdiaphragmatic pressure swings (ΔPdi) or diaphragmatic excursion measured by ultrasound during quiet breathing or during maximal inspiratory effort. (18)

Most recently, Aubier and associates showed that despite this dysfunction, there was no difference between diaphragmatic muscular contractility pre and post cholecystectomy as measured during maximal bilateral phrenic nerve stimulation. (19) They hypothesized that phrenic nerve output from the CNS was decreased as a result of an inhibitory reflex arising from sympathetic, vagal, or splanchnic abdominal receptors. Thus, decreased central output to the phrenic nerve would cause diaphragmatic dysfunction without changing the inherent contractile properties of the diaphragm. It is interesting that central drive as measured by mouth occlusion pressure($P_{0.1}$) is increased after upper abdominal surgery. (20) Probably, increased central drive in general is directed to thoracic muscles of respiration in compensation for the diaphragmatic inhibition. (20)

These studies have shown that the degree of decrease in VC and FRC after upper abdominal surgery is proportional to the risk of pulmonary complications. The decrease in VC is proportional to and caused primarily by diaphragmatic dysfunction. This dysfunction may be due to decreased phrenic nerve output rather than changes in contractility or other factors such as pain. It has been suggested that therapy for this problem might be directed to increasing central output to the diaphragm. (19)(See "Prevention of Complications" below).

Closing Volume

Why do normals as well as patients with diseased lungs and increased secretions get postoperative atelectasis and pneumonia? Closing volume (CV) in normals is somewhere between end-tidal point(FRC) and RV. It is hypothesized that because of the postoperative change in breathing pattern, i.e. small frequent breaths with elimination of sighing and reduction in FRC, end tidal point is lowered to below the CV. (3) When tidal breathing occurs below closing volume some alveoli will not be ventilated. Unventilated alveoli soon collapse after residual gas is absorbed, and bacteria proliferate rapidly in atelectatic areas. (21,22) Obese patients who already have a decreased ERV will be tidal breathing even further below their closing volume. Smokers who have a higher closing volume because of diseased airways may also be tidal breathing far below closing volume postoperatively.(See Fig 3 below from Craig (15)).

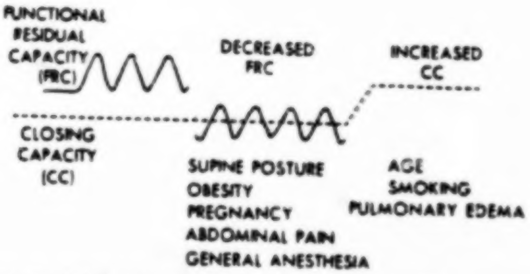


FIG 3 Relationship of CC to FRC In young healthy patients FRC normally is larger than CC (left) If FRC falls (middle), or CC rises (right), small airway closure may occur during normal breathing

Postoperative Oxygenation

Postoperative decreases in oxygenation are also most marked after upper abdominal surgery. In one study, during the first 48 hours after upper abdominal surgery, pO_2 was observed to fall 20-30% from preoperative values. There was a 10-18% drop after lower abdominal surgery and a 5-10% decrease after non-abdominal surgery. This was in the presence of routine measures to prevent atelectasis including physiotherapy and assisted coughing. (5) CO_2 retention has been noted as a problem primarily in patients with advanced lung disease who had some degree of CO_2 retention before surgery. (3) However, in one study, chronically hypercarbic patients were seen to decrease their pCO_2 in the postoperative period after lower abdominal surgery. (23) (Also see below under "Pulm. Dis.")

Mucus Transport

During anesthesia and for a prolonged period after abdominal surgery, mucus transport is impaired. Secretions made radio-opaque by tantalum powder were found not to be cleared and to subsequently pool in atelectatic segments. This problem was not observed after non-abdominal surgery. Factors which exacerbate mucus transport impairment include barbiturate or narcotic analgesia, prolonged immobilization, presence of an endotracheal tube, and of course ineffective coughing. (24)

Effects of Anesthesia

There are varying reports on whether narcotic premedication causes hypoxemia. Those that reported a decrease in pO_2 noted more of a change than could be accounted for by the slight increase in pCO_2. (25) There has been no convincing demonstration of hypoxemia secondary to atropine as a pre-medication. (25) Variable but generally mild hypoxemia and decreases in FRC are known to occur during general anesthesia, but in non-abdominal surgery lung volume changes do not persist into the post-anesthetic period. (26) Extensive reviews of physiologic changes during anesthesia are available. (25,26,27)

RISK FACTORS FOR PULMONARY COMPLICATIONS

Obesity

Assessment of risk from obesity is limited by the paucity of prospective comparative data. Reported incidence of pulmonary complications in the obese have ranged from 3.9% to 95%. (28) Dureuil reported that obese patients compared to normals had more marked decreases in VC and diaphragmatic function after upper abdominal surgery. (6) Vaughan et al noted lower baseline and postoperative oxygenation in patients undergoing jejuno-ileal bypass operations for morbid obesity, when compared to controls (29). Postoperative hypoxemia was often dangerously low in these morbidly obese patients.

In the only prospective study which defined obesity for the purpose of the study(10% above the Metropolitan life insurance tables), Latimer found that obesity was associated with a higher risk of clinically significant atelectasis after upper abdominal surgery than any other factor. (12) 53% of obese patients developed this complication while only 9% of normal weight patients did so.

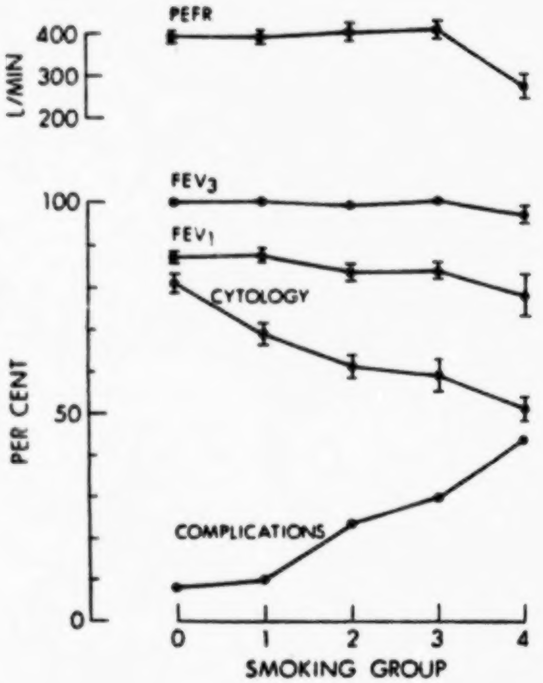
Patients with the obesity-hypoventilation syndrome have more severe cardiopulmonary derangements than those that are simply obese and thus may be at even greater risk, although this has not been proven. If the surgery is not emergent it may be prudent to postpone an operation for this group of patients, since weight loss of as little as 10-20 kg may bring about a significant improvement in pO_2, pCO_2, and somnolence. (30)

In his 1986 review of the literature on the risk of surgery in the obese, Pasulka concluded that postoperative pulmonary complications in obese patients have not been associated with grave morbidity, but that those with co-morbid disease such as COPD, advanced age, or atherosclerotic disease were at increased risk and should undergo a very careful assessment of their cardiopulmonary status. (28)

Smoking

Despite the fact that as few as 20% of smokers will quit before an elective operation when advised to do so by a physician, it is a worthwhile effort. Chalon and associates showed a relationship between the amount of current smoking, the degree of cytologic aberration in respiratory epithelium, and the incidence of postoperative complications in a prospective study of 104 asymptomatic smokers. (38) (See Figure 2 below)

FIGURE 2. Mean variations in percentages of normal cellular features, FEV_1 and FEV_3 (timed vital capacities expressed as percentage of total vital capacity forcefully expired in one and three seconds), PEFR (liters/min), and percentage of complication rate after operation in various smoking categories. O=nonsmoker (N-24), 1=light smokers (N=31), 2=moderate smokers (N=28), 3=heavy smokers (N=16), and 4=very heavy smokers (N=12). Brackets indicate ±1 SE.



In a retrospective analysis of patients undergoing coronary artery bypass grafting, Warner et al concluded that, compared to abstainers, smokers showed increased risk of pulmonary complications with 20 pack-years appearing to represent the critical level (39) (See Fig. 2 below) In addition, they found that a statistically significant decrease in complications occurred only for patients who quit smoking 8 weeks or more before surgery. (See Fig. 1 below) The differences in risk were not related to pulmonary function test results, in agreement with Chalon's study. This 8 week smoke-free minimum is consistent with studies from other investigators reviewed by Warner, which show the same time period required to effect improvement in ciliary and small airway function, closing volumes, sputum production, and tracheobronchial clearance of radiolabelled particles. (39)

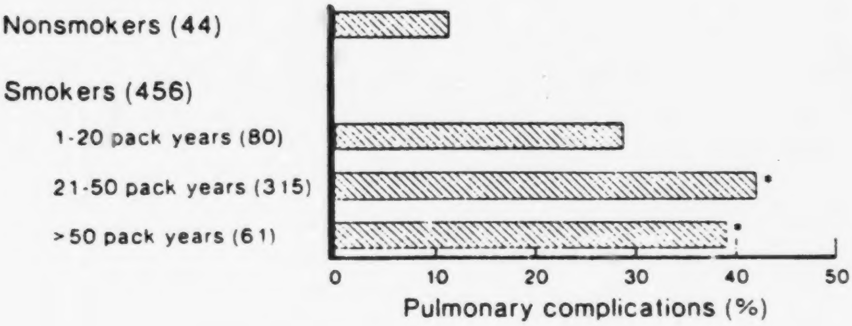


FIG. 2. Degree of smoking and pulmonary complication rates in 500 CABG patients. Degree of smoking in pack years (years × packs/day). *$P < 0.04$ compared with smokers with 1-20 pack years.

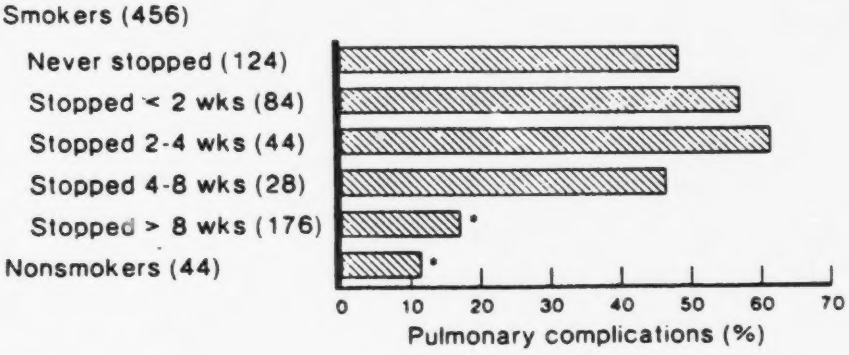


FIG. 1. Preoperative duration of moking cessation and pulmonary omplication rates in 500 CABG atients. *$P < 0.001$ compared ith patients who never stopped moking preoperatively.

Type and Duration of Anesthesia

There is no difference overall between the different anesthetic gases in regard to incidence of complications, although in one study light halothane anesthesia combined with intercostal nerve block for cholecystectomy seemed to cause the least drop in pO_2 in the immediate postoperative period. (31) Latimer et al, as well as other authors, noted an anesthesia time of greater than 3.5 hours to be associated with an increased incidence of pulmonary complications. (12) There is no difference in risk between spinal and general anesthesia, (3,23,32,33) although regional block is associated with less risk than either of these two. (3)

Surgical Factors

In addition to the differences between upper abdominal, lower abdominal, and non-abdominal surgery discussed above, there is some data suggesting that the type of incision may make a difference. Following cholecystectomy, patients with a subcostal incision had less depression of VC, less hypoxemia, and fewer complications than patients who received a midline incision. (34) In patients undergoing esophageal resection, separate laparotomy and thoracotomy incisions caused less impairment of pulmonary function than a single thoracolaparotomy incision. (35) Vertical laparotomies are associated with less atelectasis and hypoxemia than horizontal laparotomies. (36,37)

Age

Literature review articles have differed in their assessment of whether age is an independent risk factor. (3,12,40) This is understandable, when the studies from which these conclusions are drawn are examined; control groups in these studies were poorly matched and confounding variables were not accounted for. A few other studies are presented below.

Boushy et al (41) reported that of those patients who had an FEV_1 <2 liters, age greater than 60 was associated with a much higher rate of death or severe complications after thoracotomy. Another study found increased mortality with age from thoracotomy, but this was entirely dependent on an association with an abnormal EKG and MVV <60% predicted. (42) Tarhan, in his review of surgical risk in patients with COPD found no increased risk from advanced age alone. (33)

A thought provoking risk benefit analysis of thoracotomy for bronchogenic carcinoma in patients over age 70 was conducted by Yellin and Benfield. (43) They concluded that advanced age alone should not govern the decision for lung resection.

Pulmonary Disease

COPD patients have been identified as the subgroup of pulmonary patients at increased risk, as opposed to those with restrictive disease in which cough and flow rates are preserved. Various pulmonary function tests have been advocated for distinguishing low from high risk groups but no one best test has emerged.

Stein and Cassara found that patients with an FEV_1/FVC ratio of <70%, end-tidal CO_2 >45mmHg, or MEFR of <200ml/sec had a postoperative complication rate of 60%, compared to 10% for patients with all normal values. However, those with abnormal values who received an intensive preoperative regime of bronchodilators, chest percussion, and postural drainage fared better, with the complication rate falling to 21% (44).

Latimer noted a 100% incidence of pulmonary complications (many of them mild) in patients with an FEV_1/FVC ratio of <65%. (12)

Gracey and colleagues found that, in general, MVV <50% predicted, FEF 25-75 <50% predicted, and FVC <75% predicted were all predictive of a high risk of prolonged mechanical ventilation postoperatively. Failure to improve these values with 48-72 hours of preoperative preparation was a very specific indicator of high risk. (7)

Cain, (45) Milledge, (46) and Williams (47) found that the degree of abnormality in spirometric values down to an FEV_1 of 450cc was not useful in quantitating the increased risk of serious postoperative pulmonary complications in COPD patients. In Cain's study of patients undergoing abdominal or thoracic cardiovascular surgery, all four patients with a pCO_2 > 45 mm Hg had complications, two of whom died. Milledge(46) and Stein (48) also identified pCO_2 > 45-50mmHg as a sensitive and specific predictor of severe complications postoperatively. Williams stated that even patients with CO_2 retention and cor pulmonale could be supported through the postoperative period, but intra and postoperative care had to be flawless. (47) Hypoxemia in the absence of hypercapnia has been only inconsistently identified as a marker of increased risk. (7,8,45,46,49) (Also see above, "Postoperative Oxygenation")

Thus, as a result of these and other earlier studies we can say that COPD patients with abnormal PFTs are at higher risk than the normal population. However, the degree of abnormality in their PFTs is not always a reliable way to quantitate the increased risk and in fact no degree of abnormality on spirometric testing above an FEV_1 of 450cc can be called "prohibitive" for non-lung resectional surgery. However, a pCO_2 > 45-50 seems to be predictive of high risk of morbidity and mortality.

Asthma

Early studies indicated that asthmatics were at an increased risk of postoperative pulmonary complications compared to the non-asthmatic population. (50) Perioperative concerns for asthmatic patients include exacerbation of their disease, and the possibility of poor wound healing or adrenal insufficiency in steroid dependent asthmatics. Oh and Patterson showed however that even steroid-dependent asthmatics could do very well during and after major surgery as long as they received good preoperative preparation and postoperative care. (51)

Halothane has been advocated by some as the best anesthetic agent for patients with asthma because of rapid induction, lack of salivation, increased lung compliance and fewer postoperative complications. (33,51) Ketamine also has been advocated for asthmatics (52). However, some feel that the evidence for advocating either of these two agents is not convincing; some investigators have found no difference in incidence of wheezing between general and regional anesthesia in the absence of endotracheal intubation (40).

Some authorities have advocated avoidance of d-tubocurarine as it has a histamine releasing effect, but the clinical significance of this is unknown. (33) The combination of thiopental and cyclopropane was shown to be associated with an increased incidence of bronchospasm in one study. (50) It has also been suggested that "high" spinal or epidural anesthesia (above T6) may be contraindicated in patients with a history of bronchospasm as it may block sympathetic efferents to the pulmonary plexus leaving the vagal innervation unopposed. (33) Gold reported a higher incidence of complications in asthmatics who received "high" spinal anesthesia compared to "low"(below T6). (50)

Endotracheal intubation and rough handling of the viscera are probably the most common factors which precipitate bronchospasm during general anesthesia. (51)

LUNG RESECTION

Evaluation of Operative Candidacy

In evaluating patients for possible lung resection we must attempt to predict the lung function which will remain and whether that amount of function will yield an acceptable incidence of postoperative morbidity, mortality, and respiratory disability. Most institutions have come to regard a predicted postoperative FEV_1 of 800-1000cc as the minimum for operative candidacy. This value, however, has been arrived at by somewhat arbitrary means.

Early studies had indicated a high risk of postoperative complications in patients undergoing lung resection who had an MVV <50% predicted, FVC <70% predicted, RV/TLC >50%, FEV_1 <1.2-2.0 liters, or "non-specific ECG abnormalities" in combination with age >40 and MVV<50% predicted. (8) Others however found little or no predictive value in preoperative PFTs. (41,53) One 1968 study advocated denial of thoracotomy for patients with severe dyspnea after walking a 19 step flight of stairs. In this study there was a 50% mortality in 4 patients who were disabled to this degree. However, anything less than severe dyspnea was not predictive of risk (53); the problems inherent in quantitating such a subjective evaluation are obvious.

Olsen advocated the 800cc FEV_1 cutoff based on observations of the level of daily function of patients (with 2 lungs) with FEV_1 values < .8 liters and on previous work suggesting that the majority of such patients suffer from hypercapnia (54). The latter observation, however, has not been substantiated by others (8).

Nostrand (53), Kristersson, (55) Miller, (56) and others have justified use of an 800-1000cc lower limit because of an acceptable surgical mortality in patients falling above it (5-8% for pneumonectomy). The unanswered question is, what is an acceptable surgical mortality in a disease with an untreated mortality of 100%?

Predicting Postoperative FEV_1

Lung function, particularly in those with bronchogenic carcinoma, is often not symmetrical. Various methods for estimating the portion of function in the lung which will not be resected have been reported. Bronchospirometry, the oldest of these methods, involves selective intubation of each bronchus and while very accurate is now of historical interest only, because of its invasiveness and requirement for a high degree of operator skill. The lateral position test which measures changes in FRC during assumption of each lateral decubitus position is also now of historical interest as more recent studies have shown a high degree of variation in values from test to test and day to day, particularly in patients with an FEV_1 <2 liters. (8)

Two methods which have recently become popular for predicting post resection FEV_1 are xenon radiospirometry and technetium macroaggregate lung scanning. Comparison between ventilation, perfusion, or a combination of the two scans for accuracy in predicting postoperative FEV$_1$ after pneumonectomy and lobectomy was done by Wernly et al. (57) They found that the perfusion scan alone was as accurate as ventilation or combined ventilation and perfusion scans. Perfusion scanning has an advantage over ventilation scanning in that it gives better anatomic resolution. (55) The r value for correlation between predicted and actual postop FEV$_1$ was .81, and mean % error was 12% for pneumonectomy and 7% for lobectomy. (57) Similar r values for the perfusion scan were obtained by other investigators. (58,59,60)

Of several formulas which Wernly et al tested, the simplest were as accurate or more accurate than the rest, as follows.

For pneumonectomy:

$$\text{Pred. postop FEV}_1 = \text{Preop FEV}_1 \times \text{\% perfusion to "remaining" lung}$$

For lobectomy:

$$\underline{\text{Loss}} \text{ of function} = \text{Preop FEV}_1 \text{ X } \frac{\text{\# of functional segments in lobe to be resected}}{\text{Total \# of segments in both lungs}}$$

Wernly and others have felt that there is a margin of safety present in these calculations, in that when they are wrong they usually overestimate the loss of function. The exception to this generality may be in patients whose preop RV/TLC ratio is > 35%, possibly because their airspaces are already maximally dilated. (61) In this group postoperative predictions of MVV, FRC, and TLC were erroneously predicted high as often as low. (60)

In cases of lobectomy one should keep in mind that for up to three months postoperatively the level of function in the operated lung will be less than predicted. (62)

A short, elderly female does not need as large a postpneumonectomy FEV$_1$ as a tall, middle aged male. For this reason, some authorities advocate using % predicted FEV$_1$ for determinations of operability rather than an absolute value of 800cc. A proposed cutoff is an FEV$_1$ of 30% predicted. (See Table 2 below, from Gass (8)). Forthcoming studies should address this issue.

Table 2—*Use of Percent of Normal in Predicting Postpneumonectomy FEV_1*

Equation 1 Predicted Postpneumonectomy FEV_1 = Preop FEV_1 × % Function from Lung to Remain

Equation 2 Postpneumonectomy FEV_1 as % of Normal = Predicted Postpneumonectomy FEV_1 (Equation 1) ÷ Normal* FEV_1 × 100

Example Preop FEV_1 = 1.5 L, Lung Scan = 60% of Activity from Lung to Remain Normal* FEV_1 for Sex, Ht, Age = 2.0 L

Predicted Postpneumonectomy = 1.5 L × .6 = (.9 L ÷ 2.0L) × 100 = 45%

FEV_1 as % of Normal*

			How FEV_1 of .8 L^a compares to Percent of Normal*				
Sex	Age (yr)	Ht (in)	Predicted Postpneumonectomy FEV_1 (L)		Normal* FEV_1 (L)		Predicted Postpneumonectomy FEV_1 as % Normal*
Woman	70	60	.8	÷	1.658	=	48.3
Man	50	72	.8	÷	3.764	=	21.3

*Based on Morris JF, Koski A, Johnson LC. Spirometric standards for nonsmoking healthy adults. Am Rev Respir Dis 1971; 103:57-67

Other Methods of Assessing Risk of Thoracotomy

While a predicted postoperative $FEV_1 < 800$cc may serve as a minimum value for operative candidacy, many deaths and complications occur in those above this arbitrary cutoff. Boushy (41) and Keagy (63,64) found that the degree of PFT abnormality showed no correlation with morbidity or mortality post pneumonectomy or lobectomy. Also, some older studies had noted that post-pneumonectomy disability was primarily related to alterations in cardiac output and pulmonary artery pressures rather than limitations in ventilation or perfusion, a subject reviewed by Gass (8). Thus, methods have been sought which would stratify patients according to their cardiopulmonary reserve.

Hypoxemia has not been a consistent criterion of increased risk since unventilated but still perfused areas are often removed by the resection, leading to improvement in pO_2. This was borne out in Kristersson's study in which 18 of 19 patients had an increase in pO_2 post-thoracotomy averaging 10mmHg. (55) Boushy and Reichel found no significant difference in pO_2 or pCO_2 values between those with complicated vs uncomplicated postoperative courses, (41,65) although pCO_2 >45-50mmHg has been previously noted to be an ominous risk factor in general.(See above in "Pulmonary Disease")

Three studies have addressed the utility of measuring VO_2 max as a predictor of postoperative complications. Eugene et al reported a small prospective series of lung resection patients who underwent bicycle ergometer testing to determine maximum VO_2. They found that there was little relationship between preoperative PFT's and VO_2max, and that all postoperative deaths were among those with VO_2max < 1.0 liter/minute. Three of the four patients with VO_2max < 1.0 liter/min died. (66)

Colman asserted that exercise testing did not predict those who would have complications after thoracotomy, but this study was flawed by including all complications such as bleeding and empyema in the statistical analysis. (67)

Smith et al recently performed a prospective study with analysis of complications limited to those of a cardiopulmonary nature. (68) He confirmed the observation by Eugene that the degree of reduction in FEV_1 was not related to VO_2 max. Smith also found that only 1 of 10 patients with a VO_2 max > 20cc/kg/min had a complication while all six patients with a VO_2 max < 15cc/kg/min had cardiopulmonary complications. Four of six patients with VO_2 max in the 15-20cc/kg/min range had complications including one of the two deaths.

One author felt a decreased mortality rate could be achieved in those high risk patients with borderline spirometry, by not offering thoracotomy to patients who during exercise had a pO_2 of <45 mmHg and mean PA pressure of >35 mmHg in the uninvolved side. (54) This measurement involved placement of a balloon occlusion catheter in the pulmonary artery of the lung to be resected and measuring the mean PA pressure in the opposite side during exercise. However, in this study it is not clear that these measurements consistently governed the decision to operate and there was no attempt to compare a matched group who would have been considered operable except for these criteria. This technique has fallen into disfavor because of the lack of availability of these specialized catheters and the high failure rate of the technical procedure itself. (8,54)

Fee demonstrated in a study with Swan-Ganz catheter measurements that all deaths from respiratory insufficiency postoperatively were in patients who had a preoperative pulmonary vascular resistance(PVR) of > 190 dyne/sec/cm^{-5} during exercise. Three of the five patients with this high exercise PVR died. There was little relationship of PVR to PFTs. (69)

In his 1986 review of preoperative pulmonary function testing Gass expressed the opinion that using VO_2 max and PVR as determinants of operability should be limited to prospective protocols until further data are accumulated. (8)

PREVENTION OF COMPLICATIONS

Preoperative Preparations

Retrospective analyses have shown that the incidence of pulmonary complications can be reduced in patients with COPD by adjuncts such as deep breathing maneuvers, chest physiotherapy(PT), bronchodilators, and antibiotics if indicated. (33,70) Starting the regimen preoperatively rather than postoperatively is clearly more effective. (33,44,70) It is also useful to monitor improvements in pulmonary function during the preoperative "tune-up" as those who improve their PFTs have a better prognosis than those who do not. (7)

Postoperative Prophylactic Lung Expansion Maneuvers

In a recent editorial by O'Donohue, he noted more confusion than concurrence regarding the choice and use of incentive spirometry, chest PT, deep-breathing exercises, or CPAP postoperatively to prevent or decrease the incidence of pulmonary complications. (71) He notes that most postoperative atelectasis is not clinically significant and requires no specific therapy. In the subgroup of patients undergoing open heart surgery, about 90% will get left lower lobe atelectasis but only a small fraction of these will have a complication that requires specific treatment. In children after open heart surgery, postoperative chest PT was actually associated with increased pulmonary complications. (72)

A practical question is, who should get these lung expansion maneuvers prophylactically? Upper abdominal surgery is probably the most common risk factor and it is this population that has been most extensively studied. In one study, healthy patients(American Society of Anesthesiologists Class I or II) received no benefit in terms of decreased atelectasis from prophylactic hourly incentive spirometry after elective cholecystectomy. (73) Prophylactic chest physiotherapy did not decrease pulmonary complications in obese patients undergoing Roux-en-Y gastric bypass. (74)

O'Donohue states that any patient who is willing or able to take deep breaths and has an inspiratory capacity of > 1000 cc usually does not need any lung expansion procedure for preoperative or postoperative prophylaxis. (71) But if we have a patient who would be high risk by this simplified assessment, which maneuver should we prescribe? Studies comparing lung expansion maneuvers have been flawed by lack of control groups, use of the measure at intervals unlikely to have any significant beneficial effect(such as qid), and failure to measure lung volumes (to classify patients by their ability to take deep breaths and also to quantitate changes in FRC). These shortcomings notwithstanding, some recent articles are reviewed below.

Celli et al prospectively studied 172 patients undergoing abdominal surgery, comparing control group, IPPB, incentive spirometry, and deep breathing exercises. (32) All lung expansion maneuvers were performed for 15 minutes qid. There was no difference between control and treatment groups regarding incidence of roentgenographic atelectasis or consolidation. When the data was reanalyzed for upper abdominal surgery patients only, there was a significant difference in clinical complications between control and treatment groups. There was a significant decrease in hospital stay compared to control only in the incentive spirometry group. Still, overall there was no significant difference between the lung expansion maneuvers.

Stock et al prospectively compared prophylactic CPAP, incentive spirometry, and deep breathing exercises in 65 adults undergoing upper abdominal surgery. (75) There was no control group. All three maneuvers were delivered for 15 minutes every 2 hours while awake. CPAP was delivered by face mask at 7.5 cm H_2O pressure with 90 l/min bias flow. Roentgenographic evidence of atelectasis was seen at 72 hours in 23% of CPAP patients, 42% of deep breathing exercise patients, and 41% of incentive spirometry patients, differences which did not achieve statistical significance. Although the author claimed that CPAP led to more rapid improvement in FRC postoperatively, analysis of the data reveals that the CPAP patients had the greatest declines from preoperative values in the immediate postoperative period and therefore would be expected to make larger gains during the ensuing 72 hour postoperative course. Thus, there was no significant difference in effectiveness between these three methods in the prevention of roentgenographic atelectasis or improvement in FVC after upper abdominal surgery.

A Swedish study compared CPAP and positive expiratory pressure(PEP) with incentive spirometry as a "control group" in 50 patients undergoing elective upper abdominal surgery. (76) CPAP was administered for 30 breaths every waking hour at 10-15 cm H_2O pressure. PEP was administered at the same frequency by a face mask with the valve set to operate at 10-15cm H_2O pressure. Incentive spirometry was also administered for 30 breaths every hour while awake. There were statistically significant improvements in FVC and oxygenation, and a decreased incidence of clinically significant atelectasis in patients who received CPAP or PEP compared to the "control group" of incentive spirometry. They concluded that PEP showed particular promise as a postoperative lung expansion maneuver since it is cheap, easily portable, and can be used without supervision.

An excellent review of all aspects of chest physiotherapy was recently published. (77) Although not specifically directed to pre and postoperative concerns the authors stated that in general chest physiotherapy was not useful and may even be detrimental except in treatment of lobar atelectasis or in conditions characterized by sputum production in excess of 30cc/day.

Other Preventive Measures

Getting the patient out of bed into a chair will increase his FRC by 10-20%, and facilitate sighing and deep breathing. (11)

Diaphragmatic dysfunction after upper abdominal surgery was discussed above, and it was stated that therapy of this problem might be directed toward increasing central output to the phrenic nerve. Animal studies have shown that aminophylline stimulates respiratory center output to the diaphragm. (78) In addition, a recent clinical study by Dureuil et al demonstrated that diaphragmatic function after upper abdominal surgery was significantly improved by aminophylline. (79) Although we are far from recommending theophylline as prophylaxis for anyone undergoing upper abdominal surgery, these studies provide further support for its use in the perioperative management of patients with lung disease.

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INHALATION INJURY

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INTRODUCTION

Burns and burn-related injuries comprise a significant clinical problem with which all critical care physicians should be familiar. In the United States alone, burn injuries account for up to 108,000 hospital admissions, and up to 12,000 patients suffer burn-related deaths annually (1). Of these burn-related deaths, approximately 50% are due to pulmonary insufficiency, even though inhalation injury is noted to occur in only 8 to 36% of burn victims (2-5); this associated mortality rate is not artifactual, since the probability of inhalation injury doesn't parallel burn severity. Thus inhalation injury is an especially lethal complication of burns, and deserves special attention when caring for these patients.

HISTORICAL PERSPECTIVES

The fatal nature of inhalation injury was first documented by the Roman historian Pliny the Elder (AD 23-79) who in his account of the Second Punic War (218-201 BC), described the execution of prisoners by placing them in cages above greenwood fires. The Cleveland Clinic fire of 1929 claimed scores of lives due to smoke inhalation. (The pathology in those victims was similar in some respects to silo-filler's disease, since nitrogen dioxide was generated by burning nitrocellulose x-ray film.) In 1942, a fire at the Coconut Grove nightclub resulted in 114 casualties. Seventy-five of these patients were dead on arrival at the Massachusetts General Hospital from smoke inhalation; of the remaining 39 patients only 3 were free of respiratory symptoms, and all 7 subsequent fatalities were due to respiratory complications (6). The description of the pulmonary complications of the Coconut Grove fire laid the groundwork for the further systematic study of inhalation injury.

INCIDENCE OF INHALATION INJURY

In two large recent studies of inhalation injury, and a smaller study of inhalation injury in motor vehicle accidents, the reported incidence of inhalation injury ranged from 8.6 to 35% (3-5). The range of values reported is a reflection of the populations studied. Shirani reported an incidence of 35%, with 73% of those patients being injured in a closed space. Purdue reported inhalation injury in 16.3% of patients burned in motor vehicle accidents.

Burn injury in a closed space is a well known risk factor for inhalation injury. Other recognized risk factors for inhalation injury include: advanced age, increased size of surface burn, the presence of facial burns, unconsciousness, burns associated with plastic fires, and steam explosions. Although each of these risk factors has limitations, the presence of any one should alert the clinician that inhalation injury may be present.

MECHANISMS OF INJURY

Inhalation injury of the tracheobronchial tree may occur by either the direct transfer of thermal energy, or by chemical injury secondary to toxic compounds present in inhaled smoke. Of the two, chemical injury is by far the more common cause.

Inspired by the report of the Coconut Grove fire, Moritz reported the effects of inhaled heat on the lungs in 1945 (7). Dogs were allowed to inhale superheated air, a blow-torch flame, and steam. The pharynx and larynx were protected to prevent rapid death from upper airway obstruction. The authors found that superheated air and even a raw flame had little effect on the lower airway. Air has a poor thermal carrying capacity and is rapidly cooled in the airway by saturation with water. Steam, which has roughly 4000 times the thermal carrying capacity of air, resulted in severe injury to the trachea and larger bronchi. The smaller bronchi and alveoli were spared injury. Recent authors have supported the findings of Moritz (3-9). Thermal injury results in severe upper airway injury resulting in obstruction at the level of the vocal cords. Because of the poor heat carrying capacity of air and because of reflex closure of the vocal cords, lower airway thermal injury is rare, but may occur with inhalation of particulate matter and with steam injuries.

Chemical injury to the tracheobronchial tree is the most common mechanism of lower airway and parenchymal damage in inhalation injuries. An understanding of the atmosphere generated by modern fires is essential to appreciate chemical inhalation injuries. Closed space combustion results in a rapid depletion of oxygen producing an FiO2 of 10 to 15%. This relatively "anaerobic" environment is the result of oxygen consumption and displacement of oxygen by fire-related gases. These gases are responsible for chemical injury to the tracheobronchial tree. Additionally, carbon monoxide levels rapidly rise in a closed space fire. Levels of carbon monoxide have been reported to reach 571,440 ppm in closed space fires (10). The maximal tolerable level of carbon monoxide is 75 ppm. Severe inhalation injury may result in cabon monoxide asphyxia in 30 minutes; such asphyxia rarely occurs in open fires where carbon monoxide levels are markedly lower.

The chemical toxins produced by fires are numerous. Acrolein, an aldehyde produced from combustion of wood or cellulose, denatures proteins and results in bronchial injury and pulmonary edema. Hydrochloric acid is liberated by burning plastics and has effects similar to acrolein. In addition, nitrogen dioxide, hydrogen sulfide, phosgene and sulfur dioxide contribute to bronchial mucosal and parenchymal injury in smoke inhalation victims. In some fires, metabolic toxins such as cyanide and arsenic compounds are produced (10-11).

In contrast to the rapid appearance of upper airway injury seen with thermal injury, chemical injury has a gradual and progressive onset, and signs and symptoms are often delayed for 24 to 48 hours post-injury.

ANATOMY OF INHALATION INJURY

The distribution of lung damage in inhalation injury in general decreases from the upper airway to the alveoli. The upper airway, major bronchi, and terminal bronchioles are involved in 60%, 30% and 10% of patients respectively (8). In another review, major airway injury was found in 26% and terminal airway injury in 19%, with diffuse injury noted in 55% of patients (12). As noted above, thermal energy, as well as soluble gases such as sulfur dioxide, hydrogen chloride and ammonia, produce upper airway injury. Volatile insoluble gases and soluble gases attached to carbon particles are responsible for lower tract injury. Hypoxemia, with the attendant increase in minute ventilation, and smoke containing benzene, which anesthetizes the airway, both promote lower airway injury (13).

Pathologically inhalation injury may be divided into distinct stages. During the initial 12 hours mucosal irritation and erythema occur and may be associated with bronchospasm. Upper airway obstruction at the level of the false cords may occur with severe injury. Ventilation may be further compromised by the presence of chest wall eschar, which may lead to alveolar hypoventilation. From 12 to 24 hours pulmonary vascular constriction and decreased cardiac output may lead to increased deadspace ventilation although with modern methods of fluid resuscitation this is now uncommon. From 224 to 48 hours mucosal edema and ulceration occur. Sloughing of tracheobronchial mucosa and pseudomembrane formation results in obstructive physiology. At approximately 48 hours pulmonary edema occurs, which is often multi-factorial in origin. Depending on the severity of inhalation injury, surfactant loss and capillary leak may occur leading to decreased pulmonary compliance and increased shunt. After 72 hours patients are at an increased risk of pneumonia secondary to the loss of normal lung defenses (2,8,10,11). On microscopic examination the lungs show congestion of the alveolar walls with intra-alveolar, interstitial and septal edema.

Alveolar capillary proliferation is present, and fibrin capillary thrombi have been described.

Several investigators have studied extravascular lung water (EVLW) in inhalation injury (12,15-16). Head demonstrated a pulmonary capillary leak, using an indocyanine green method, that was not associated with a generalized capillary leak syndrome secondary to hypoproteinemia. Tranbaugh found EVLW increased in 6 of 14 patients but capillary leak was felt to be etiologic in only 1 patient. The remaining patients had developed congestive failure or pneumonia. Herndon in an animal model demonstrated increased pulmonary lymph flow and increased transvascular protein leak. On balance, the increase in EVLW in inhalation injury occurs as a result of both capillary leak and hydrostatic forces, and both factors are probably operative in most patients.

CLINICAL APPROACH

In caring for burn victims, the possibility of inhalation injury should always be considered, since in many patients the onset of symptoms is insidious. In performing the history and physical, one should note the presence or absence of the risk factors mentioned earlier, even though these risk factors may be misleading, e.g. 25% of patients injured in closed areas will not have inhalation injury. Blast injury, once thought to rarely cause inhalation injury, may produce inhalation injury in as many as 25% of cases. Only 24% of those with burned nasal hairs, and 66% of those with facial burns are found to have inhalation injury; carbonaceous sputum is much more specific, but is seen in only 50% of patients with inhalation injury (17). A high index of suspicion must be maintained.

If inhalation injury is suspected the clinician must address several questions immediately. Is there evidence of carbon monoxide toxicity? Is there evidence of upper airway obstruction? Is there severe airway and parenchymal damage, with the risk of early respiratory failure? Tables 1 and 2 (appendix) outline the clinical signs and symptoms of inhalation injury and carbon monoxide poisoning.

DIAGNOSTIC STUDIES

The limitations of the clinical diagnosis of smoke inhalation and the high mortality of inhalation injury have spawned interest in early diagnosis.

Arterial blood gases are of little utility in the early diagnosis of inhalation injury. Typically the PaO2 is normal early, and decreases as inhalation injury becomes manifest at 12 to 24 hours post injury. The A-aDO2 becomes abnormal early but is not specific for inhalation injury. It is important to realize that the PaO2 in inhalation injury may not accurately reflect hemoglobin saturation, since high levels of carboxyhemoglobin may be present in the face of a normal PaO2.

Elevated carboxyhemoglobin levels are associated with a higher incidence of inhalation injury (8). However, the severity of injury cannot be predicted reliably, because most patients are treated with oxygen prior to arriving at the burn center, and because the chemical constituents of smoke don't show a consistent relationship with carbon monoxide content.

The radiographic manifestations of inhalation injury are well described. In the majority of patients the chest radiograph is initially normal. Following a latent period of at least 12 hours, atelectasis, lobar collapse, pulmonary vascular congestion, pulmonary edema and pneumonia may all be seen (18-19). The pathophysiology of these findings has been previously discussed.

Several investigators have attempted to use the chest radiograph in the early diagnosis of inhalation injury (20-21). Teixidor, in a non-blinded and retrospective study, evaluated 56 patients with inhalation injury. Patients with cardiogenic pulmonary edema were excluded. Thirty-five patients were found to have radiographic abnormalities, 31 of these in the first 24 hours. Five patients had alveolar edema, 21 had mixed alveolar and interstitial edema, and 9 patients had either "perivascular fuzziness" or peribronchial cuffing as an early indicator of inhalation injury. Haponik attempted to serially measure the vascular pedicle width on chest x-ray as an indicator of early pulmonary edema. Unfortunately, this method was technically poossible in only 42 of 191 patients who were eligible for the study; furthermore, a widened vascular pedicle is only present when pulmonary edema is associated with volume-overload states. While the chest radiograph is useful in the total assessment of the burn patient, the 12 to 24 hour latent period makes it an insensitive early indicator of inhalation injury.

The 133-Xenon ventilation/perfusion scan is a sensitive early indicator of inhalation injury, and is usually positive within 4 hours post injury. Intravenously injected or inhaled Xenon is normally cleared from the lungs within 90 seconds. Delayed washout or localization of Xenon correlates well with inhalation injury. False positive scans may be seen in COPD, asthma, and bullous disease. 133-Xenon scanning has a sensitivity of 90%, a specificity of 87% and an accuracy of 87%. When combined with bronchoscopy, which alone has a diagnostic accuracy of 86%, the diagnostic accuracy rises to 93%. Combining 133-Xenon scanning, bronchoscopy and pulmonary function testing results in a diagnostic accuracy of 96% (22).

As noted above, bronchoscopy has a diagnostic accuracy of 86%, although it is not routinely performed. Typical findings include airway hyperemia and edema, and soot deposition.

Pulmonary function testing may be useful in selected patients in following the progression of inhalation injury. Bedside spirometry is the most useful and practical technique. The utility of PFT's is limited by the clinical condition of the patient and the presence of concomitant facial injuries or burns.

The PFT abnormalities in burn patients were well described by Whitener (23). PFT's were performed in burn patients with and without inhalation injury, and in patients who had suffered inhalation injury without surface burns. In the patients with surface burns FVC and TLC were both decreased. The initial decrease correlated best with the extent of burn and the presence of chest burns reflecting thoracic cage restriction. Subsequent decreases correlated with increases in body weight, which presumably reflects increases in lung water. RV was normal or reduced in surface burn patients again reflecting restrictive physiology. The inhalation only group demonstrated predominantly obstructive physiology. RV was increased in this group and the inhalation only group showed the most severe decrease in the FEV-1/FVC ratio. Airway inflammation and mucus plugging by sloughed tracheobronchial mucosa account for these findings.

Haponik used serial flow-volume measurements and serial nasopharyngoscopy to monitor the progression of upper airway edema in inhalation injury (24). Predictably, patients requiring intubation showed a decrease in serially measured values, and no patient with stable flows required intubation. Of note, patients who had minimal findings on initial nasopharyngoscopy, but who subsequently required intubation, had significantly decreased initial flows compared with patients not requiring intubation. The authors concluded that physiologic abnormalities precede anatomic ones. They also noted that progression of upper airway edema correlated with the percent of surface burn, the presence of facial burns and the rate of fluid administration.

Increased dead space ventilation has recently been reported as a consequence of inhalation injury. Pulmonary angiograms were normal, and microvascular thrombi were proposed to be responsible (25).

THERAPY

As in all critically ill patients, inhalation injury patients must have a secure airway, adequate ventilation, and support of circulation when necessary.

Asphyxia accounts for up to 50% of pre-hospitalization burn deaths, and is commonly secondary to carbon monoxide or cyanide poisoning. Carbon monoxide produces asphyxia by displacing oxygen from hemoglobin, while cyanide poisons the cytochrome oxidase system. Carbon monoxide poisoning is treated with 100% oxygen, which decreases the half-life of carboxyhemoglobin from 4 hours to approximately 40 minutes. For carboxyhemoglobin levels in excess of 60% hyperbaric oxygen therapy is recommended. Cyanide intoxication is treated by the infusion of 300mg of sodium nitrite over 2 to 4 minutes. This produces methemoglobin which binds cyanide to form cyanomethemoglobin. Sodium thiosulfate, 12.5 grams, is then infused over 10 minutes. This converts cyanomethemoglobin to hemoglobin and thiocyanate, which is then excreted.

Upper airway obstruction must be managed aggressively, and prophylactic intubation is recommended if any of the following are seen: early supraglottic inflammation and edema on endoscopy, progressive hoarseness, early or progressive hypoxemia ($PaO2$ <60 torr on a 40% O2mask), tachypnea, or hypercarbia with a $PaCO2$ > 45 torr. Some authors recommend the prophylactic application of CPAP or PEEP to prevent post-intubation capillary leak (26-27), since the loss of the glottic expiratory retard could theoretically increase the risk of transudation across pulmonary capillaries.

The treatment of lower airway and parenchymal injury is multifactorial. Adequate oxygenation and ventilation must be assured. This often requires mechanical ventilation with the application of PEEP. Best PEEP should be selected on the basis of oxygen delivery. Pulmonary artery catheters should be used if needed, with an awareness of the potential infectious complications. Pulmonary toilet with periodic suctioning is essential; the use of bronchodilators should be dictated by the presence of bronchospasm. Broad spectrum antibiotics should be used when there is any suspicion of pneumonia. Corticosteroid therapy is contraindicated in burn patients, since it has been associated with increased mortality and an increased risk of sepsis (28).

MORBIDITY AND MORTALITY

Most of the major pulmonary complications of inhalation injury have been described earlier. Pneumonia is a common complication which occurs earlier in inhalation injury patients than in burn patients without inhalation injury. It may be seen as early as 48 to 72 hours in inhalation injury, as opposed to 5 days in burns alone. The incidence of pneumonia increases with increasing body surface area burned (5). Cardiac and non-cardiac pulmonary edema are the next most frequent complications, and have been discussed. Other complications include pneumothorax, atelectasis, tracheal stenosis, bronchial stenosis, bronchiolitis obliterans, and bronchiectasis.

The overall mortality for inhalation injury ranges from 50% to 60%; it is increased at the extremes of age, and also is increased with more extensive surface burns. Early mortality is secondary to asphyxia, airway obstruction, circulatory collapse and cardiac failure, with late mortality frequently secondary to pulmonary sepsis.

TABLE 1. Symptoms and signs of inhalation of products of combustion

CNS	Dizziness, headache, confusion, seizures, hallucinations, coma
Respiratory	Tachypnea, cough, hoarseness, stridor, dyspnea, retractions, wheezing, sooty sputum, chest pain, tightness, rales/ rhonchi
Facial	Singed nasal hairs, soot in oropharynx, facial burns
Cardiac	Arrhythmias

Note: Overlap with manifestations of CO intoxication may be seen

TABLE 2: Clinical manifestations of carbon monoxide poisoning (3)

Carboxyhemoglobin Level	Symptoms
< 20%	Headache, dyspnea, confusion, lapse of attention, loss of peripheral field of vision
20% to 40%	Irritability, faulty judgment, dim vision, nausea, vomiting, easy fatigue
40% to 60%	Tachycardia, tachypnea, confusion, hallucinations, ataxia, syncope, convulsions, coma
> 60%	Often fatal

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CHEST TRAUMA

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INTRODUCTION

Chest trauma is a very broad topic encompassing many areas ranging from injuries to the bony thorax and vascular structures to inhalation injuries and radiation pneumonitis. This discussion is directed primarily to the subject of blunt (non-penetrating) chest trauma with resultant injury to the bony thorax, pleural space and lung parenchyma. Particular emphasis is placed upon the topics of flail chest/pulmonary contusion and tracheobronchial disruption.

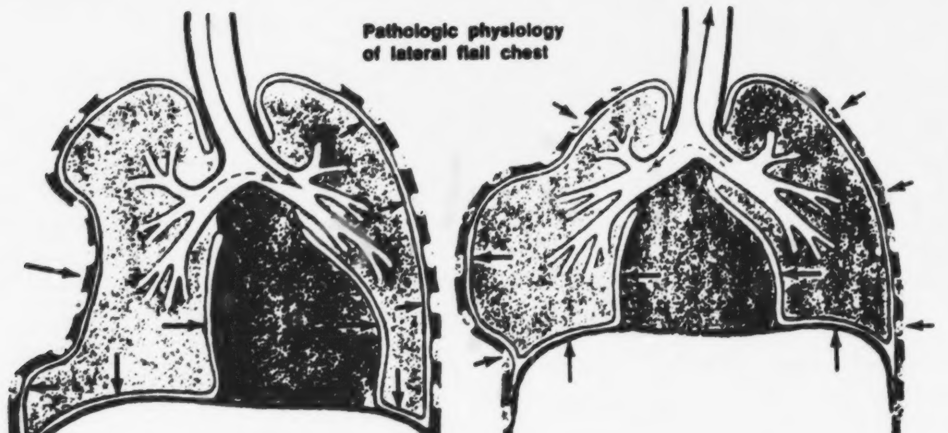
In today's mobile society, approximately 23% of all civilian deaths due to trauma are secondary to thoracic trauma. Surprisingly, however, only 15% of all patients presenting with thoracic trauma require a thoracotomy (1). The remaining patients require resuscitative measures such as tube thoracostomy and management of other concurrent injuries. Non-penetrating injuries are the most lethal form of thoracic trauma, as they are associated with an increased incidence of more serious multisystemic injuries. Proposed mechanisms of intrathoracic injury include inertial mechanisms, the spalling effect and implosion (3). The movement of structures underlying the impacted area results in the generation of different momentums (inertial forces) for each structure dependent upon its specific gravity. These different momentums result in disruptive intrathoracic shearing forces. The disruptive effects generated by compressive forces at gas-liquid interfaces in lung tissue are referred to as spalling phenomena. Lastly, implosion is defined as the rapid expansion of air bubbles (alveoli) in a liquid (lung parenchyma) after a compressive wave. This may partially explain the mechanism of pneumothorax in blunt chest trauma in the absence of rib fractures.

INJURIES TO THE BONY THORAX

Injuries to the bony thorax are similar to that of the skull in that the state of the bony framework does not always correlate with the degree of damage to the underlying viscera. The most frequent chest injuries are rib fractures (5). Rib fractures resulting from anterior-posterior compression result in a "spring fracture" and are seldom associated with underlying lung damage (7). Rib fractures resulting from a direct blow are associated with an increased incidence of lung injury secondary to the protruding rib ends. Ribs 4 through 9 are the most common site of fracture. Fracture of ribs 1 through 3 correlate with an increased incidence of major vascular and tracheobronchial injuries (6). Injuries to ribs 10, 11 and 12 are associated with an increased incidence of damage to the spleen, liver and diaphragm. The morbidity associated with simple rib fractures results from atelectasis and secondary pneumonitis. The treatment of simple rib fractures should be directed at pain control with either oral medications or with intercostal nerve blocks in order to allow normal excursion of the thoracic cage with inspiration.

One of the most controversial topics in chest trauma is the management of the patient with a flail chest syndrome. Flail chest is defined as the paradoxical movement of the chest wall, most commonly the lateral chest wall, secondary to multiple rib fractures. The paradoxical chest wall movement prevents the development of adequate negative intrathoracic pressure. Patients with flail chest injuries have an associated mortality of up to 40% (4). Areas of controversy in the management of flail chest include the use of mechanical ventilation, steroids and fluid management.

Several theories have emerged to explain the ventilatory dysfunction associated with the flail chest syndrome. Initially the German concept of a Pendelluft phenomenon was used to explain the hypoxia associated with a flail chest. According to this theory, there is a to-and-fro movement of air between the lungs during the respiratory cycle with subsequent ineffective ventilation secondary to increased respiratory deadspace (5). The affected patients are then unable to compensate with an increased minute ventilation due to painful rib fractures. One basic tenet of this theory is that the flail segment results in a pressure gradient between the two hemithoraces which results in the to-and-fro air movement during the respiratory cycle. The Pendelluft phenomenon is graphically presented below.



Inspiration

As chest expands and diaphragm descends, flail section sinks in, impairing ability to produce negative intrapleural pressure. Mediastinum and trachea shift to uninjured side, decreasing expansion capability of lung on that side

Expiration

As chest contracts and diaphragm rises, flail segment bulges outward, impairing expiratory effect. Mediastinum and trachea shift to injured side. In severe flail chest air may shuttle uselessly from one lung to the other as indicated by broken lines (pendelluft)

The Pendelluft phenomenon is currently not accepted as a valid explanation for the ventilatory dysfunction associated with the flail chest syndrome. Pulmonary contusion underlying the flail segment is the most widely accepted explanation for the ventilatory impairment associated with flail chest. This will be further discussed later in this article.

Before 1956, flail chest injuries were managed by external stabilization. External stabilization was accomplished by several different methods including strapping the flail segment, sandbagging the flail segment and counter-traction techniques. Occasionally internal operative stabilization with the placement of intramedullary pins was used in refractory cases (5). In 1956, with the advent of mechanical ventilation, Avery et al introduced the concept of "internal pneumatic stabilization" (12). Using a volume cycled ventilator, these authors proposed that patients with a flail segment benefited from controlled positive pressure ventilation until the rib injuries stabilized. For the next twenty years this was the accepted mode of therapy for flail chest injuries. Another ancillary supportive procedure used at that time was tracheostomy. The proposed beneficial effect of tracheostomy was to reduce the ventilatory deadspace and airway resistance thereby allowing more air exchange at smaller pressure gradients (7). The reduced pressure gradient required for ventilation resulted in less paradoxical chest wall motion during respiration. In an often quoted article by Trinkle et al published in The Annals of Surgery in 1975, the authors challenged the belief held at that time that "internal pneumatic stabilization" was the only effective method of treating flail chest injuries (8). They proposed that the chest wall instability was a minor part of the respiratory defect in the majority of flail chest patients. They felt that the degree of underlying pulmonary contusion better explained the respiratory defect. Trinkle's study was a retrospective review of 30 patients admitted to Bexar County Hospital between 1972 and 1974 with a history of moderate to severe blunt chest trauma resulting in a flail chest syndrome. The patients were divided into two groups. There were 19 patients in Group I. These patients were admitted to the anesthesiology unit and treated with early tracheostomy and mechanical ventilation. Group II consisted of 11 patients who were admitted to the cardiothoracic unit and treated only as if they had a pulmonary contusion. The treatment regimen for Group II patients included fluid restriction, methylprednisolone 500 mg QID for three days, colloid fluid replacement therapy, vigorous pulmonary toilet, aggressive chest wall pain control with morphine and intercostal nerve blocks as needed, and positive pressure ventilation for room air PaO_2's <60mmHg. The conservatively treated group (Group II) had fewer complications (20% versus 100%), a lower mortality (0% versus 20%), and shorter stays in the intensive care unit (1.6 days versus 22.6 days). The conclusion of this retrospective analysis was that when flail chest is managed with mechanical ventilation and tracheostomy, the morbidity and mortality associated with these interventions exceeds that of therapy directed only at the underlying contusion. This study, though often quoted as the basis for the "selective management" of flail chest injuries, has several major flaws including non-randomized patient selection and non-comparable patient populations. However, the article did serve to alter the method in which flail chest injuries were managed as more emphasis was placed on the importance of the underlying pulmonary contusion. Another often quoted study by Shackford, published in 1981, concurred with Trinkle's hypothesis that treatment in flail chest should be directed at the underlying contusion and not the chest wall deformity (10).

The best study documenting acceptable therapeutic outcomes when flail chest/pulmonary contusion is managed "selectively" was published by Richardson et al in 1982 (12). This was a prospective study whereby patients with blunt chest trauma were not intubated except under the following circumstances: 1) hypoxemia and respiratory distress (PaO_2 <55mmHg on room air or PaO_2 <60mmHg with supplemental oxygen), 2) major associated injury, 3) necessity for general anesthesia, and 4) airway obstruction. Of a group of 427 patients, 95 patients had a flail chest injury. Only 50% of the flail chest patients were intubated; of those, 69.5% were intubated less than three days. Basic management principles included resuscitation with crystalloids as needed; steroids were not used. Important points noted by this author best summarize the current management strategy of flail chest: 1) Routine tracheostomy and mechanical ventilation in patients with a flail chest/pulmonary contusion leads to an unacceptably high incidence of nosocomial infections and respiratory complications. 2) Vigorous pulmonary toilet and pain control are the mainstays of therapy. 3) Avoid relegating non-mechanically ventilated patients to lower levels of nursing and medical care as close monitoring is very important in the management of these patients.

Two other controversial management points in flail chest/pulmonary contusion include the use of steroids and the choice of resuscitative fluid. Trinkle et al, as noted previously, used steroids in their therapy of flail chest/pulmonary contusion. No control studies exist to demonstrate that steroids are efficacious in this condition and in fact steroids have been shown to reduce the rate of bacterial clearance from the lung (14). Trinkle et al in a dog study in 1973 reported that the use of balanced salt solutions as a resuscitative fluid resulted in a more serious and progressive contusion abnormality. The proposed mechanism was one of "hemodilution" whereby the crystalloid solutions lowered the plasma oncotic pressure which potentiated the contusion abnormality. Bongard in 1984 reviewed Trinkle's study and noted several criticisms including lack of control animals, large fluid volumes (90 cc/kg in 4 hours) and contradictory study findings. In Bongard's review of 28 patients with pulmonary contusion, he plotted PaO2/FiO2 ratios compared to calculated plasma oncotic pressure. No significant correlation between the two values was found in either the survivors or the non-survivors. His findings contradict the assumption that hemodilution is a contributing factor to the hypoxemia and tend to support the use of crystalloids, as needed, as a resuscitative fluid.

While pulmonary contusion is a common complication of flail chest, it can also result from trauma in the absence of significant chest wall injuries. Radiographically, pulmonary contusion presents as peripheral non-anatomic infiltrates. They are usually progressive lesions which may not present radiographically for a period of up to 6 hours after the injury. Findings are typically localized to the area of injury, but contrecoup injuries have been noted. Radiographic resolution is rapid, usually complete within 48 to 72 hours (6). Pathologically the lung parenchyma demonstrates a disrupted microvasculature with interstitial extravasation of RBCs and alveolar flooding. A closed glottis at the time of impacting increases the likelihood and severity of pulmonary contusion (7). Dog studies have demonstrated that contused lungs have a slower rate of bacterial clearance.

In summation, the morbidity and mortality of flail chest injuries continues to be high, although the associated injuries probably predict outcome better than the flail injury itself (14). At the present time, the "selective" management of these injuries appears appropriate.

INJURIES INVOLVING THE PLEURAL SPACE

Blunt chest trauma may result in several types of injury to the pleural space. Most notable among these injuries are pneumothorax, tension pneumothorax, hemothorax and chylothorax.

Pneumothorax is common in the setting of significant chest injuries, being found in 30% of patients who present with blunt chest trauma and nearly all of those with penetrating trauma. Actually, today the most common etiology for pneumothorax is trauma of another nature - iatrogenic. Commonly quoted incidences of iatrogenic pneumothorax are as follows (30):

Etiology	Incidence
-Mechanical Ventilation	4%
--COPD	8%
--Intubation Rt. mainstem	13%
--PEEP	15%
--Aspiration pneumonia	37%
-Fine needle aspirate	18-24%
-Transbronchial biopsy	5.5%
-Pleural biopsy	3%
-Thoracentesis	2%

In blunt chest trauma, pneumothoraces are occasionally associated with a rib fracture in which the ribs lacerate the visceral pleura. The majority, however, are not associated with a fracture. The proposed mechanism in this setting involves traumatic compression of the alveoli with resultant dissection of air from the alveoli into the interstitium, resulting in dissection into the mediastinum with leak into the pleural space. The treatment of choice for pneumothoraces secondary to blunt chest trauma is tube thoracostomy.

Tension pneumothorax is an uncommon complication of blunt chest trauma, however, it may occasionally present in the setting of a tracheobronchial disruption with an associated tear in the mediastinal pleura which creates a one way valve. A tension pneumothorax may also be a complication of mechanical ventilation (7).

Emergent management of a tension pneumothorax is essential with the most expedient form of therapy being the creation of an open pneumothorax by the insertion of a catheter in the second intercostal space anteriorly. This allows equalization of pleural space pressure with atmospheric pressure. Untreated, a tension pneumothorax is rapidly fatal due to ventilatory impairment, because of loss of functioning lung parenchyma secondary to compression, and inability of the thoracic bellows to generate a negative pressure gradient.

Large pneumothoraces and tension pneumothoraces are usually readily diagnosed; however a pneumothorax in a critically ill supine patient may easily be missed. Ziter et al reviewed the subject of detection of a pneumothorax in the supine patient and noted six radiographic findings which were useful in this setting (24). The findings noted were as follows: (32 patients).

Radiographic finding	Incidence
-Basilar hyperlucency	100%
-Double diaphragm sign	84%
-Sharply outlined lower cardiac border	72%
-Depressed diaphragm	66%
-Apical pericardial fat pads	38%
-Inferior edge of collapsed lung	31%

Hemothorax is defined as a post-traumatic pleural effusion with a hematocrit greater than 50% of the peripheral value (28). Hemopneumothorax is found in 62% of patients presenting with nonpenetrating chest trauma and evidence of a pneumothorax. Hemothorax is associated with a 49% incidence of mortality in blunt chest trauma and is indicative of severe co-existing injuries. Only 25% of patients presenting with hemothorax have significant enough blood loss to result in shock. Blood may enter the pleural space as a result of injuries to the systemic vessels such as the aortic arch, or the intercostal, bronchial, or internal mammary arteries. It is unusual to have a significant hemothorax from lung parenchymal bleeding as the pulmonary arterial circulation is a low pressure system with a mean PA pressure of approximately 15 mm Hg (1). Traumatic hemothorax can be successfully managed with tube thoracostomy alone in 70 to 95% of cases (2). Indications for open thoracotomy include "massive bleeding", defined as a total blood loss of 1000cc to 1500cc or continued blood loss of greater than or equal to 300ml/hr for 2 or 3 hours. The complications associated with hemothorax include residual blood in the pleural space, empyema (1 to 4%), persistent pleural effusion (31%) and fibrothorax (1%) (28). The management of residual clotted blood in the pleural space has been controversial. In the past, the recommended management had been early thoracotomy to evacuate any residual clotted blood (decortication) to prevent early (empyema) and late (fibrothorax) pleural sequelae. Wilson et al challenged this practice in an article published in the Journal of Thoracic and Cardiovascular Surgery in 1979 (29). The study included 452 patients with chest trauma (penetrating and non-penetrating) and hemothorax. The patients were grouped into 3 groups as below with the following results.

Group 1A: no residual hemothorax after tube thoracostomy
Group 1B: residual hemothorax after tube thoracostomy
Group II: patients who underwent thoracotomy for reasons other than hemothorax

RESULTS

Group	patients	cases empyema(%)	abn Cxr
IA	290	14 (4.8%)	11%
IB*	118	6 (5.1%)	16%
II	44	2 (4.4%)	49%

* 1 patient required decortication

As can be seen, Wilson found no increased incidence of empyema in the presence of a persistent hemothorax. Additionally, fibrothorax requiring decortication was rare. Shock, gross contamination of the pleural space and prolonged pleural drainage correspond with an increased incidence of empyema. There is an increased incidence of fibrothorax in the presence of empyema and hemopneumothorax (28). Currently it is justified to manage residual hemothorax conservatively monitoring for evidence of infection and/or respiratory impairment.

Chylothorax is an uncommon complication of trauma which results from a disruption of the thoracic duct, allowing chyle to enter the pleural space. It usually presents as a non-irritating pleural effusion with resultant dyspnea. The most common cause of chylothorax is malignancy which accounts for 50% of the cases. Trauma, penetrating, nonpenetrating, and surgical, account for 25% of cases with the remaining cases being idiopathic (15%) and from miscellaneous causes (10%) (23). Chylothorax resulting from non-penetrating chest trauma usually results in a right pleural effusion 2 to 10 days after the injury. The thoracic duct in this instance is usually disrupted in the area of the ninth or tenth thoracic vertebrae. First the chyle collects in the mediastinum, often appearing as a posterior mediastinal mass or chyloma, and then ruptures into the pleural space. Chyle is a nonirritating bacteriostatic substance. Between 1500 cc and 2500 cc of chyle is emptied into the venous system daily. The diagnosis of chylothorax should be suspected when an odorless milky appearing fluid is aspirated at the time of thoracentesis. The diagnosis can be confirmed by several methods including: 1) triglyceride content greater than 110 mg/dl, 2) lipoprotein analysis of fluid demonstrating chylomicrons, and 3)ingestion of a lipophilic dye (Cosmetic Green #6) which stains the pleural effusion. Complications associated with chylothorax include fibrothorax, immunologic dysfunction secondary to lymphocyte depletion, and malnutrition, as chyle is a substance rich in protein and fat (7). Prior to 1948 when Lampson performed the first successful thoracic duct ligation, chylothorax had an associated mortality of approximately 50%. Today with operative and non-operative therapy, the mortality associated with this condition has improved considerably. The treatment goals in chylothorax include drainage (tube thoracostomy) and maintenance of the nutritional and immunological status. After tube thoracostomy, in the majority of cases, the disrupted area of the thoracic duct closes spontaneously. In order to facilitate early closure, attempts are made to reduce the rate of chyle formation and lymph movement. This can be accomplished by dietary alterations and limiting mobility of the lower extremities, which are associated with slower lymph flow (7). Dietary manipulations include limiting oral intake and dietary supplementation with a TPN solution containing medium chain triglycerides. If conservative therapy fails and chyle drainage persists beyond 7 days, pleurodesis with tetracycline may be attempted (23). If pleurodesis fails, surgical intervention with thoracic duct ligation is warranted (27). Often the site of thoracic duct disruption is difficult to localize. Techniques to aid localization include lymphangiography and dye injections.

PARENCHYMAL LUNG INJURIES

Three relatively unusual complications of nonpenetrating chest trauma are tracheobronchial disruption, pulmonary hematomata, and traumatic lung cysts. This final section is devoted to a discussion of these interesting but rare findings. Pulmonary contusion has already been discussed under flail chest injuries.

Tracheobronchial disruption is an uncommon complication of chest trauma. It has an associated mortality of 30% (17). The key to diagnosis is a high level of suspicion in trauma victims. Methods of clinical presentation are numerous including complete unilateral atelectasis (late finding), mediastinal and subcutaneous emphysema, pneumothorax with persistent air leak (50%), tension pneumothorax (~25%), and massive hemoptysis (7). Up to 50% of the patients in one study presented with no other injuries other than tracheobronchial disruption (16). Eighty percent of injuries involve the mainstem bronchi (right greater than left), 15% involve the trachea and 5% involve the distal bronchi (17). Injuries involving the trachea are located in the membranous portion and result in a vertical tear. The hypothesized mechanisms of injury include: 1) compression of the tracheal air column against the thoracic spine with a closed glottis resulting in a "blow out" injury and (2) development of shearing forces at points of tracheal fixation with resultant tracheobronchial injury. Findings which should spur further evaluation include: 1) pneumothorax with "fallen lung sign" whereby the collapsed portion of the lung falls inferiorly, 2) deep cervical emphysema, 3) "cut off sign" at site of fractured bronchus, and 4) rib fractures involving ribs 1 through 3 (6,17,18). Fifty-three percent of patients with tracheobronchial disruptions have rib fractures involving one of the first three ribs (6). When one of the latter signs or symptoms is present in a blunt trauma victim, bronchoscopy should be performed to rule out an injury to the trachea or the endobronchial tree and to establish the site, nature, and extent of injury (26). If an injury is confirmed and involves greater than 1/3 of the bronchial circumference, immediate thoracotomy and surgical repair is indicated (19). If surgical intervention is inadvisable then the insertion of an endotracheal tube beyond the area of transection should be accomplished. Excellent operative results have been noted in 90% of cases (7). Occasionally with severe disruption, surgical resection of the affected lobe is indicated. Tears involving the smaller bronchi tend to seal spontaneously and do not require surgical intervention. Occasionally after prolonged periods of time (years) bronchial disruptions have been discovered with complete bronchial stenosis and post-obstructive atelectasis. In one case a successful reanastomosis was accomplished 15 years after the injury (17). In summary, the key to making a diagnosis of tracheobronchial injury is to have a high index of suspicion in the patient who presents with blunt chest trauma and one of the above mentioned signs and symptoms (which are relatively common in the multiply injured patient).

Pulmonary hematomas are another uncommon finding after thoracic trauma. They result from the accumulation of extravasated blood in a space created by parenchymal disruption. Radiographically they often first appear as an ill-defined infiltrate, but as surrounding areas of pulmonary contusion resolve a 2 to 5 cm mass appears. They are typically located posteriorly in the lower lobes and on occasion may be associated with contrecoup injuries. They resolve over a period of 2 to 4 weeks. The diagnosis is one of exclusion.

Traumatic lung cysts or traumatic pneumatoceles result from a pulmonary laceration with hemorrhage and entry of air from disrupted alveoli and small bronchioles. They are most commonly found in patients under the age of 30 (80%) who present with blunt chest trauma (21). They may occur in any location, however the apices are often spared. Initially their presence may be obscured by an overlying pulmonary contusion. Neoplastic causes must be excluded. Rarely the cysts may become secondarily infected (21). Their radiographic resolution follows that of a pulmonary hematoma, only with a more protracted course. The cavity normally heals completely in 2 to 16 weeks.

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